Division of Transplant and Ophthalmology Products Advisory Committee Meeting Briefing Package

for

Aflibercept injection for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD)

Applicant:
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Introduction and Background

VEGF Trap (aflibercept injection) is a recombinant protein consisting of specific domains of the human VEGF receptors, VEGF-R1 and VEGF-R2, fused to an IgG1 Fc. VEGF Trap is a specific antagonist that binds and inactivates circulating VEGF and PlGF in the blood stream and in the extravascular space. In comparison, pegaptanib injection (Macugen) is an inhibitor of the VEGF165 isomer and ranibizumab injection (Lucentis) and bevacizumab (Avastin), are inhibitors of all VEGF-A isomers. Therefore, VEGF Trap not only inhibits all isoforms of VEGF-A, but also inhibits PlGF.

Drug Established and Proposed Trade Name, Drug Class, Applicant's Proposed Indication, and Dosing

Proposed Proprietary Name:	Eylea
Established name:	aflibercept injection
Pharmacologic Category:	VEGF inhibitor
Proposed Indication:	Treatment of patients with neovascular (wet) age-related macular degeneration (AMD)
Dosage Form and Route of Administration:	intravitreal injection

Currently Available Treatments for Proposed Indication

NDA/BLA	Drug	Approval	Indication
N/A	Thermal laser photocoagulation	N/A	Laser therapy to close abnormal leaking vessels, however rarely used currently.
NDA 21-119	Photodynamic therapy (PDT)/ Verteporfin	April 2000	Indicated for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to AMD, pathologic myopia, or POHS.
NDA 21-756	Macugen (pegaptanib injection)	December 2004	Indicated for the treatment of neovascular (wet) age-related macular degeneration
BLA 125-156	Lucentis (ranibizumab injection)	June 2006	Indicated for the treatment of patients with neovascular (wet) age-related macular degeneration

Chemical Composition

Drug Product Formulation Used in Clinical Trials

Component	Formulation Composition	
	ITV-1	ITV-2
Aflibercept	5, 10, 20, 40 mg/mL	10 and 40 mg/mL
Sodium phosphate, (b) (4) (b) (4)	10 mM sodium phosphate	10 mM sodium phosphate
Sodium phosphate (b) (4) (b) (4)		
Sodium chloride	135 mM	40 mM
Sucrose	none	5 % (w/v)
(b) (4)		
Polysorbate 20	none	0.03% (w/v)
(b) (4)		

Pre-filled Syringes
Pre-filled syringes were developed to improve the ease of drug delivery for physicians. This delivery method was studied in one clinical trial VGFT-OD-0702 in 99 patients. Only limited long term stability data is available for the pre-filled syringes.

Vials
For some earlier trials both ITV-1 and ITV-2 formulations were used. Vials with ITV-2 formulation were used in both VIEW #1 and VIEW #2. The volume of injection is 50 µL (0.05 mL) for the 0.5 mg dose of VEGF Trap-Eye and the 2 mg dose of VEGF Trap-Eye. The study drug is withdrawn using aseptic technique through a filter needle attached to a 1 mL syringe. The needle is then aseptically removed from the syringe and replaced with a 30 gauge needle for the intravitreal injection.

Description of Clinical Data Sources

Study	Phase	Study Design	Objective	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Status
VGFT-OD-0603	1	Double-masked, randomized with open-label expansion cohort	Study designed to assess the safety and tolerability of 2 formulations of VEGF Trap-Eye (IVT-1 and IVT-2). Studied the following for 12 weeks: 4mg Q4 IVT-1 4mg Q4 IVT-2 4mg Q4 open label IVT-2 After 12 weeks patients received 4mg prn	20	AMD	12 weeks	Completed
VGFT-OD-0502	1	Part A-Phase 1, open-label dose escalation Part B-Randomized, double-masked, active controlled Part C-Randomized, double-masked	The first study in which VEGF Trap-Eye was IVT administered to subjects with AMD. This study comprised 3 single-dose sub-studies (parts A, B, and C) and enrolled a total of 51 subjects. Each of the single-dose periods in parts A, B, and C was followed by a treatment-free, extended follow-up period lasting up to 1 year. Studied doses of aflibercept ranging from 0.05mg-4mg	51	AMD	57 days (primary analysis) and continued up to 12 months	Completed
VGFT-OD-0702	Extension Phase 1/2	Single masked, randomized to compare pre-filled syringe (PFS) vs. vial	Subjects who completed VGFT-OD-0508, VGFT-OD-0603, or VGFT-OD-0502 were given the opportunity to enroll in this long-term extension study. This is an ongoing study designed to provide long-term safety information (beyond 1 year) on the use of VEGF Trap-Eye 2 mg, administered on an as needed (prn) basis. It also provides comparative safety information for 2 delivery modes of VEGF Trap-Eye: vials (as administered to subjects in the phase 3 pivotal trials) and pre-filled syringes (PFS).	157	AMD	38 months	Active but not recruiting.

Study	Phase	Study Design	Objective	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Status
			VGFT Trap-Eye 2mg prn (PFS)-99 patients VGFT Trap-Eye 2mg prn (vials)-50 patients				
VGFT-OD-0508 (CLEAR-IT AMD-2)	Phase 2 dose ranging	Randomized, double-masked	Obtain safety and efficacy data for 5 parallel dosing groups of VEGF Trap-Eye: - 0.5 mg q12 weeks (32 patients) - 0.5 mg q4 weeks for 12 weeks (32 patients) - 2.0 mg q12 weeks (31 patients) - 2.0 mg q4 weeks for 12 weeks (31 patients) - 4.0 mg q12 weeks (31 patients) Beginning at Week 16, subjects in all treatment arms were evaluated every 4 weeks for subsequent PRN dosing at the randomized dose level.	159	AMD	12 weeks (primary endpoint) continued to 52 weeks	Completed
VIEW #1 (VGFT-OD-0605)	Phase 3	Double-masked, randomized, active controlled	Designed to obtain safety and efficacy data for four parallel treatment groups: Ranibizumab q4 weeks (306 patients) VEGF Trap-Eye 2.0 mg q4 weeks (304 patients) VEGF Trap-Eye 0.5 mg q4 weeks (304 patients) VEGF Trap-Eye 2.0 mg q8 weeks (313 patients)	1217	AMD	52 weeks (primary endpoint) continued to 96 weeks	Ongoing, 52 weeks complete for all patients
VIEW #2 (311523)	Phase 3	Double-masked, randomized, active controlled	Designed to obtain safety and efficacy data for four parallel treatment groups: Ranibizumab q4 weeks (303 patients) VEGF Trap-Eye 2.0 mg q4 weeks (313 patients) VEGF Trap-Eye 0.5 mg q4 weeks (311 patients) VEGF Trap-Eye 2.0 mg q8 weeks (313 patients)	1240	AMD	52 weeks (primary endpoint) continued to 96-100 weeks	Ongoing, 52 weeks complete for all patient
VGFT-OD-0910	Phase 3 extension of VIEW 1	Open label	Long term safety and tolerability 2mg capped prn (at least every 12 weeks)	178 (as of 9/15/10). Target is 960 patients.	AMD	18 months	Ongoing

Aflibercept has also been studied in patients with DME, CRVO, and oncology indications. This main support for safety and efficacy for the AMD indication comes from the following trials: VIEW #1, VIEW #2, and VGFT-OD-0702 and will therefore be the focus of this review.

Discussion of Individual Trials

VIEW #1

Study VGFT-OD-0605: "A Randomized, Double-Masked Active Controlled Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap-Eye in Subjects with Neovascular AMD"

Short Title: VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 1)

Primary Objective: The primary objective of this study is to assess the efficacy of intravitreally administered of VEGF Trap-Eye compared to ranibizumab (in a non-inferiority paradigm) in preventing moderate vision loss in subjects with all sub-types of neovascular AMD.

This is an ongoing randomized, double-masked, active controlled, multi-center, phase 3 study conducted in the US and Canada. The study consists of a 21-day screening period followed by clinic visits and IVT injections of study drug administered every 4 or 8 weeks (including sham injections at interim study visits when study drug was not administered) for 52 weeks (total of 16 visits) during the first year of the study. No sham injections were given at week 52. The entire study duration is approximately 2 years (96 weeks plus the recruitment period). During the second year of treatment, subjects will be evaluated every 4 weeks and will receive IVT injections of study drug at intervals determined by specific dosing criteria, but at least every 12 weeks. During the second year of treatment, sham injections will not be given. During this period, injections may be given as frequently as every 4 weeks, but no less frequently than every 12 weeks, according to specific pre-specified re-dosing criteria. The pre-specified criteria are:

- Increase in central retinal thickness >=100 microns compared to lowest previous value as measured by OCT
- A loss from the best previous letter score of >=5 ETDRS letter in conjunction with recurrent fluid as indicated by OCT
- New or persistent fluid as indicated by OCT
- New onset classic neovascularization
- New or persistent leak on FA
- New macular hemorrhage
- 12 weeks has elapsed since the previous injection

The results are based on the data obtained between start of enrollment and the data cut-off point for each individual subject at the week 52 visit when the primary endpoints of this study were obtained. The period covered in the first 52 weeks for VIEW #1 is 8/2/07 (first subject's first dose) to 9/14/10 (last subject's last visit for the primary endpoint) for year 1. The study is currently ongoing for the second year as planned while masking is maintained for subjects and personnel involved in the study.

On day 1, subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:

1. 2 mg VEGF Trap-Eye administered every 4 weeks (2Q4)
2. 0.5 mg VEGF Trap-Eye administered every 4 weeks (0.5Q4)
3. 2 mg VEGF Trap-Eye administered every 8 weeks (2Q8) plus a sham injection at interim 4-week visits (when study drug was not administered), following 3 initial monthly doses
4. 0.5 mg ranibizumab administered every 4 weeks (RQ4)

Inclusion Criteria:

1. Signed informed consent
2. Men and women ≥ 50 years of age
3. Active primary subfoveal choroidal neovascularization (CNV) lesions secondary to AMD, including juxtafoveal lesions that affected the fovea as evidenced by FA in the study eye
4. CNV must be at least 50% of total lesion size
5. ETDRS BCVA of: 20/40-20/320 in the study eye
6. Willing, committed, and able to return for all clinic visits and completed all study-related procedures
7. Understand and willing to sign the ICF

Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins
3. Prior treatment with anti-VEGF agents as follows:
    a. Prior treatment with anti-VEGF therapy in the study eye was not allowed
    b. Prior treatment with anti-VEGF therapy in the fellow eye with an investigational agent (not FDA approved, ie. bevacizumab) was allowed up to 3 months prior to first dose in the study, and such treatments were not allowed during the study. Prior treatment with an FDA/Health Canada approved anti-VEGF therapy in the fellow eye was allowed.
    c. Prior systemic anti-VEGF therapy, investigational or FDA/Health Canada approved was only allowed up to 3 months prior to first dose, and was not allowed during the study.
4. Total lesion size > 12 disc areas (DAs) (30.5 squared mm, including blood, scars and neovascularization) as assessed by FA in the study eye
5. Subretinal hemorrhage that was either 50% or more of the total lesion area, or if the blood was under the fovea and was 1 or more DAs in size in the study eye (if the blood was under the fovea, then the fovea must have been surrounded 270 degrees by visible CNV).
6. Scar or fibrosis, making up > 50% of total lesion in the study eye
7. Scar, fibrosis, or atrophy involving the center of the fovea
8. Presence of RPE tears or rips involving the macula in the study eye
9. History of any vitreous hemorrhage within 4 weeks prior to visit 1 in the study eye
10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema (DME) or any other vascular disease affecting the retina, other than AMD, in either eye
12. Prior vitrectomy in the study eye
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye
14. Any history of macular hole of stage 2 and above in the study eye
15. Any intraocular or periocular surgery within 3 months of day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as it was unlikely to interfere with the injection
16. Prior trabeculectomy or other filtration surgery in the study eye

17. Uncontrolled glaucoma (defined as IOP ≥25 mmHg despite treatment with anti-glaucoma medication) in the study eye
18. Active intraocular inflammation in either eye
19. Active ocular or periocular infection in either eye
20. Any ocular or periocular infection within the last 2 weeks prior to screening in either eye
21. Any history of uveitis in either eye
22. Active scleritis or episcleritis in either eye
23. Presence or history of scleromalacia in either eye
24. Aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of an YAG posterior capsulotomy) in the study eye
25. Previous therapeutic radiation in the region of the study eye
26. History of corneal transplant or corneal dystrophy in the study eye
27. Significant media opacities, including cataract, in the study eye which might interfere with VA, assessment of safety, or fundus photography
28. Any concurrent intraocular condition in the study eye (ie. cataract) that, in the opinion of the investigator, could have required either medical or surgical intervention during the 96 week study period
29. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could have either increased the risk to the subject beyond what was to be expected from standard procedures of intraocular injection, or which otherwise may have interfered with the injection procedure or with evaluation of efficacy or safety
30. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might have affected interpretation of the results of the study or rendered the subject at high risk for treatment complications
31. Participation as a subject in any clinical study within the 12 weeks prior to day 1
32. Any systemic or ocular treatment with an investigational agent in the past 3 months prior to Day 1
33. The use of long acting steroids, either systemically or intraocularly, in the 6 months prior to Day 1.
34. Any history of allergy to povidone iodine
35. Known serious allergy to the fluorescein sodium for injection in angiography
36. Presence of any contraindications indicated in the FDA approved label for ranibizumab
37. Females who were pregnant, breastfeeding, or of childbearing potential, unwilling to practice adequate contraception throughout the study. Adequate contraceptive measures included oral contraceptives (stable use for 2 or more menstrual cycles prior to screening); IUD; Depo-Provera; Norplant System implants; bilateral tubal ligation; vasectomy; condom or diaphragm plus either contraceptive sponge, foam or jelly

VEGF Trap-Eye was supplied by Regeneron Pharmaceuticals, Inc. and was administered by intravitreal injection using standard ophthalmic techniques. Sham injections for the 2Q8 group were performed using a syringe without a needle with no active drug and without intraocular penetration. All VEGF Trap-Eye study medication and sham treatments were packaged in identical packaging with identical labeling, except for the kit number. An unmasked investigator performed the study drug or sham injection. The unmasked investigator was responsible for the receipt, tracking, preparation, destruction, and administration of study drug, as well as safety assessments at 30 to 60 minutes post-IVT-injection. A separate masked physician assessed AEs and supervised the masked assessment of efficacy. All other study site personnel were required

to remain masked to treatment assignment in order to allow for an unbiased assessment of VA, safety, and ancillary study measures.

Treatment failure during the first 52 weeks of the study was defined as a decrease from baseline in BCVA by 15 or more letters at 2 consecutive assessments, 4 weeks apart. A subject who qualified as a treatment failure could be, but was not required to be, discontinued from the study. If a subject did withdraw, he or she was required to complete the Year 2 end-of study/early termination visit procedures.

Study Schedule View #1

WEEK	Screen	Day 1	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
VISIT	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
	D –21 to D 0															
Sign Informed Consent	X															
Medical/Ophthalmic History	X															
Physical Exam	X															
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NEI VFQ-25[2]	X[2]					X[2]			X[2]			X[2]				X[2]
ECG/NYHA	X															X
Interval History (AEs & Con Meds)[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect Ophthal/Slit Lamp	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP[3]	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
VA (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT	X[4]	X	X[6]	X	X[6]	X	X[6]	X[6]	X	X[6]	X[6]	X	X[6]	X[6]	X[6]	X
Fundus Photo/ FA	X[5]								X							X
Hematology & Chemistry Panel[7]	X					X			X			X				X
Serum Beta-HCG	X															
PT/PTT[7]	X															
Urinalysis/UPCR[7]	X					X			X			X				X
Serum for antibody[7]	X					X			X			X				X
Study Drug or Sham Injection[8]		X		X	X	X[10]	X	X[10]	X	X[10]	X	X[10]	X	X[10]	X	O[11]
Telephone Safety Check[9]				X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9,10]

1. AEs were to have been recorded from the time the IC was signed until completion. If a subject withdrew, AEs were recorded until withdrawal or 30 days after the last dose of study drug, whichever was later.

2. NEI VFQ-25 was administered by certified personnel at a contracted call center. Site assisted the subject at the screening visit to initiate the first call to the call center to collect all of the subject's contact information and to complete the first VFQ on the phone prior to randomization and IVT injection; the call center initiated subsequent contact at appropriate visits to complete questionnaire.

3. IOP was measured pre-dose and 30-60 minutes post-injection

4 & 5. Both eyes at screen visit

6. Optional at this visit.

7. Sample was drawn prior to administration of study drug.

8. See Study Drug Administration (protocol Appendix D [Appendix 1.1]) for study drug injection protocol

9. Mandatory telephone safety checks 3 days post injection or sham injection.

10. Subjects assigned to the VEGF Trap-Eye 2Q8 group received sham injections at these visits. A telephone safety check was mandatory after this visit.

11. Optional injection if study eye met specific criteria: increase in central retinal thickness of ≥ 100 µm compared to the lowest previous value as measured by OCT , or a loss from the best previous letter score of ≥5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT, or new or persistent fluid as indicated by OCT, or new onset classic neovascularization, or new or persistent leak on FA, or new macular hemorrhage, or 12 weeks had elapsed since the previous injection)

Study Schedule View #1 - continued

Table 3 Schedule of Events (Year 2) (continued)

WEEK	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96
VISIT	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 25	Visit 26	Visit 27
Medical/Ophthalmic History											
Physical Exam											
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
NEI VFQ-25[2]					X						X
ECG/NYHA											X
Interval History (AEs & Con Meds)[1]	X	X	X	X	X	X	X	X	X	X	X
Indirect Ophthal/Slit Lamp[5]	X	X	X	X	X	X	X	X	X	X	X
IOP[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
VA (ETDRS)	X	X	X	X	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X	X	X	X	X
Fundus Photo/ FA					X						X
Hematology & Chemistry Panel[4]					X						X
Urinalysis/UPCR[4]					X						X
Serum for antibody[4]					X						X
Study Drug Injection[5,6]	O[6]	O[6]	O[6]	O[6]	O[6]	O[6]	O[6]	O[6]	O[6]	O[6]	O[6,8]
Telephone Safety Check[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]

1. AEs should be recorded from the time the IC has been signed until completion. If a subject withdraws, AEs should be recorded until withdrawal or 30 days after the last dose of study drug, whichever is later.
2. NEI VFQ-25 will be administered by certified personnel at a contracted call center who will call the subject on the phone to complete the questionnaire.
3. Measure IOP pre-dose and 30-60 minutes post-injection.
4. Draw sample prior to administration of study drug.
5. See Study Drug Administration (protocol Appendix D [Appendix 1.1]) for study drug injection protocol.
6. Optional injection if study eye meets specific criteria (increase in central retinal thickness of ≥100 µm compared to the lowest previous value as measured by OCT, or a loss from the best previous letter score of ≥5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT, or new or persistent fluid as indicated by OCT, or new onset classic neovascularization, or new or persistent leak on FA, or new macular hemorrhage, or 12 weeks have elapsed since the previous injection).
7. Telephone safety check is required for all subjects, regardless of whether an injection was administered.
8. Dosing at visit 27 is optional for all subjects.

Primary efficacy variable: Proportion of subjects who maintained vision at week 52, where a subject was classified as maintaining vision if he/she lost fewer than 15 letters in ETDRS letter score compared to baseline.

Secondary efficacy variables:

- Change from baseline in BCVA as measured by ETDRS letter score at week 52
- Proportion of subjects who gained at least 15 letters of vision from baseline to week 52
- Change in total NEI VFQ-25 score from baseline to week 52
- Change in CNV area from baseline to week 52

Additional efficacy variables:

- Change from baseline in BCVA at week 12
- Change from baseline in CRT (central retina thickness) at week 52
- Proportion of subjects who lost 15 or more letters of vision ("moderate" vision loss) at week 52
- Proportion of subjects who gained 30 or more letters of vision at week 52
- Proportion of subjects who lost 30 or more letters of vision ("severe" vision loss) at week 52

- Change from baseline in scores for NEI VFQ-25 subscales (near activities, distance activities, vision dependency) at week 52
- Change from baseline in total lesion area as assessed by FA at week 52
- Proportion of subjects with VA of 20/40 or better at week 52
- Proportion of subjects with VA of 20/200 or worse at week 52
- Proportion of subjects who gained ≥ 0 letter of vision at week 52
- Proportion of subjects who gained 10 or more letters of vision at week 52
- Change from baseline in classic CNV area at week 52
- Proportion of subjects showing complete resolution of FA leakage at week 52
- Change from baseline in area of fluorescein leakage as assessed by FA at week 52

VIEW #2

Study 311523: "A Randomized, Double-Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap-Eye in Subjects With Neovascular AMD"

Short title: VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW #2)

Primary Objective: To assess the efficacy of intravitreally administered VEGF Trap-Eye compared to ranibizumab (in a non-inferiority paradigm) in preventing moderate vision loss in subjects with all subtypes of wet AMD.

This is an ongoing multi-center, double-masked, randomized (1:1:1:1), active-controlled, parallel-group phase 3 study in 186 centers in 26 countries. The study duration is 2 years. The current submission provides the data up to the primary endpoint covering the first 52 weeks (Year 1) of the study.

On Day 1, eligible subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:

1. 0.5 mg VEGF Trap-Eye administered every 4 weeks (0.5Q4)
2. 2 mg VEGF Trap-Eye administered every 4 weeks (2Q4)
3. 2 mg VEGF Trap-Eye administered every 8 weeks (2Q8) plus a sham injection at interim 4-week visits (when study drug was not administered), following 3 initial monthly doses.
4. 0.5 mg ranibizumab administered every 4 weeks (RQ4)

Subjects assigned to 2Q8 were to receive the 2 mg injection every 8 weeks with one additional dose at Week 4 and were to receive sham injections at interim monthly visits (ie. every 8 weeks) during Year 1 of the study. Sham injections using a mock procedure including pressure on the eye exerted by a syringe without a needle, were performed without intraocular penetration and thus without injection of any substance. The primary endpoint assessments were conducted at Week 52 before any injections were made during this visit.

As per protocol, the data were analyzed as soon as the Week 52 data for all subjects were available and cleaned, although the study is still ongoing. The Year 2 safety and efficacy assessments will continue under masked conditions. Special precautions were taken and all efforts are made to keep investigators, subjects, and study monitors masked. Only one eye per subject was enrolled in the study. If a subject's fellow (non-study) eye required treatment for

AMD at study entry, or during the subject's participation in the study, the fellow eye was allowed to receive any approved treatment (this was not allowed for the study eye). Although the fellow eye may have received treatment, it was not considered an additional study eye. Subjects who received treatment for the fellow eye could remain in the study. Safety of the fellow eye was monitored, and systemic AEs were collected.

The drug formulation and procedure of administration of drug and sham were identical to VIEW #1.

Inclusion and Exclusion criteria-Identical to VIEW 1

VIEW #2 is being conducted in the following countries (number of study centers in brackets): Argentina (6), Australia (7), Austria (3), Belgium (1), Brazil (4), Colombia (4), Czech Republic (5), France (10), Germany (21), Hungary (4), India (15), Israel (10), Italy (14), Japan (15), Latvia (2), Mexico (7), Netherlands (4), Poland (7), Portugal (2), Singapore (4), Slovakia (2), South Korea (6), Spain (16), Sweden (3), Switzerland (4), and United Kingdom (10).

Study Schedule View #2

Procedures	Screening Phase	Treatment Phase														Primary Endpoint Year 1
WEEK	Screening	Baseline	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
VISIT	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
DAY	–21 to 0	1														
Informed consent, inclusion/exclusion criteria, demographic data	X															
Medical/ophthalmic history	X															
Physical examination	X															
Vital signs (temperature, blood pressure and pulse)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NEI VFQ-25[1]	X[1]					X[1]			X[1]			X[1]				X[1]
EQ-5D health questionnaire	X															X
ECG/NYHA before dosing	X		X													X
Interval history (AEs & concomitant medications)[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy (assess pre- and post-dose)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
BCVA using ETDRS chart	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus photo/FA	X								X							X
DNA blood sampling (optional)		X[13]														
Hematology & chemistry panel[4]	X					X			X			X				X
Serum pregnancy test	X															
Prothrombin time/PTT and INR[4]	X															
Urinalysis/UPCR[4]	X					X			X			X				X
Serum for antibody[4]	X					X			X			X				X
Examination by an ENT specialist[14]		X				X										X
Randomization		X[6]														
PK blood sampling prior to injection		X[11]	X	X		X									X[11]	X[12]
Study drug or sham injection[7]		X		X	X	X[8]	X	X[8]	X	X[8]	X	X[8]	X	X[8]	X	O[9]
Telephone safety check[5]		X		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5, 8]

Procedures	Treatment Phase										End of Study[15]
WEEK	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96/100
VISIT	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 25	Visit 26	Visit 27
Vital signs (temperature, blood pressure and pulse rate)	X	X	X	X	X	X	X	X	X	X	X
NEI VFQ-25[1]					X						X
EQ-5D health questionnaire											X
ECG/NYHA											X
Interval history (AEs & concomitant medications)[2]	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy (assess pre- and post-dose)	X	X	X	X	X	X	X	X	X	X	X
Slit lamp	X	X	X	X	X	X	X	X	X	X	X
IOP[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
BCVA using ETDRS chart	X	X	X	X	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X	X	X	X	X
Fundus photo/FA					X						X
Hematology & chemistry panel[4]					X						X
Urinalysis/UPCR[4]					X						X
Serum for antibody[4]					X						X
PK blood sampling prior to injection	X[13]										
Study drug injection[7,9]	O[9]	O[9]	O[9]	O[9]	O[9]	O[9]	O[9]	O[9]	O[9]	O[9]	
Telephone safety check[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	
End of study											X

AE = Adverse event; ECG/NYHA = Electrocardiogram/New York Heart Association; ETDRS = Early treatment diabetic retinopathy study; NEI VFQ-25 = National eye institute 25-item visual function questionnaire; FA = Fluorescein angiography; IOP = Intraocular pressure; IVT = intravitreal; OCT = Optical coherence tomography; INR = International normalized ratio; PTT = Partial thromboplastin time; UPCR = urine protein creatinine ratio. Visit schedules may deviate by ±3 days. Scheduled visits should not be altered due to the deviation of the previous visit.

1 NEI VFQ-25 to be administered in a quiet room by a person certified to administer the questionnaire.
2 Baseline findings (before the first administration of study drug) and AEs (after the first administration of study drug) should be recorded from the time the informed consent has been signed until completion. If a subject withdraws, AEs should be recorded until withdrawal or 8 weeks after the last dose of study drug, whichever is later.
3 Measure IOP pre-dose and 30-60 minutes post-injection.
4 Draw/collect sample prior to administration of study drug.
5 Mandatory telephone safety checks 3 days post injection or sham injection.
6 Randomization into the study is recommended to occur prior to Visit 2. Randomization number will be assigned by an unmasked physician or an unmasked designee as soon as eligibility criteria are met.
7 See Attachment 14.1 of the study protocol for study drug injection protocol. For further details on drug administration of ranibizumab, which should also serve as a guidance for the administration of VEGF Trap-Eye, refer to the EU Commission/locally approved label for ranibizumab, which is provided in section 2.3 of the Investigator Site File and Section 5.2.2 of the study protocol. Details will also be provided in the study manual.
8 Subjects assigned to the VEGF Trap-Eye 2Q8 group will receive sham injections at these visits. A telephone safety check is mandatory after this visit.
9 Optional injection if study eye meets specific criteria (Increase in central retinal thickness of ≥ 100 µm compared to the lowest previous value as measured by OCT, or a loss of ≥ 5 ETDRS letters from the best previous letter score in conjunction with recurrent fluid as indicated by OCT, or new onset classic neovascularization, or new or persistent leak on FA, or new macular hemorrhage, or 12 weeks have elapsed since the previous injection).
10 If optional injection is performed the telephone safety check must be completed. Telephone safety check is still required if no injection was administered.
11 PK blood samples will be drawn prior to injection and 1 to 4 hours post injection at this visit.
12 If optional injection is not given, PK sampling may be taken at anytime during the visit.
13 Although DNA blood sampling should be done preferably at Baseline visit, it can also be done at a later visit, but no later than at Visit 6.
14 A standardized medical history will be taken concerning chronic airway diseases, prior to study treatment at Visit 2 by an ENT specialist. A careful endoscopy of the nasal airways with a standardized documentation of findings is completing the rhinological investigation of Visit 2. At Visit 6 and at Visit 16, the participants will be reevaluated by an ENT specialist and a nasal endoscopy will be performed.
15 Week 96 in subjects who did not receive an injection within the last 8 weeks prior to Visit 27.
Week 100 in subject who received an injection at Visit 26. An extra interim visit should be performed in these subjects at Week 96.

Primary efficacy variable: Proportion of subjects who maintained vision at Week 52, where a subject was classified as maintaining vision if the subject had lost fewer than 15 letters in the ETDRS letter score compared to baseline.

Secondary efficacy variables:

- Change from baseline in BCVA as measured by ETDRS letter score at Week 52
- Proportion of subjects who gained at least 15 letters of vision from baseline to Week 52
- Change in total NEI VFQ-25 score from baseline to Week 52
- Change in CNV area from baseline to Week 52

Additional efficacy variables:

- Change from Baseline in BCVA at Week 12
- Change from Baseline in central retinal thickness at Week 52
- Proportion of subjects who gained 30 or more letters of vision from Baseline on the ETDRS chart at Week 52
- Proportion of subjects who lost 30 or more letters of vision from Baseline on the ETDRS chart ("severe" vision loss) at Week 52

- Change from Baseline in scores for NEI VFQ-25 subscales (near activities, distance activities, vision dependency) at Week 52
- Change in scores of the EQ-5D questionnaire from screening at Week 52
- Change from Baseline in total lesion area as assessed by FA at Week 52
- Change from Baseline in greatest linear diameter of lesion on FA
- Proportion of subjects with VA of 20/40 or better at Week 52
- Proportion of subjects with VA of 20/200 or worse at Week 52
- Proportion of subjects who gained ≥ 0 letters of vision at Week 52
- Proportion of subjects who gained 10 or more letters of vision at Week 52
- Change from Baseline in classic CNV area at Week 52
- Proportion of subjects showing complete resolution of FA leakage at Week 52
- Change from Baseline in area of fluorescein leakage as assessed by FA at Week 52

Study VGFT-OD-0702: "A Randomized, Single-Masked, Long-Term, Safety, and Tolerability Study of Intravitreal VEGF Trap-Eye in Subjects with Neovascular Age-Related Macular Degeneration"

VGFT-OD-0702 was a single-masked (to the subject), randomized, multi-center clinical study. Subjects were eligible if they had neovascular AMD and completed dosing in VGFT-OD-0502, VGFT-OD-0508, or VGFT-OD-0603 to enroll in this 3 year study to assess the long-term safety and tolerability of repeated IVT administration of VEGF Trap-Eye in subjects with all sub-types of neovascular AMD. Subjects were initially enrolled to receive VEGF Trap-Eye from a Vial. After 152 subjects had been enrolled, a PFS syringe was introduced as a result of Protocol Amendment 1. From that point, upon enrollment, subjects were randomly assigned in 2:1 ratio to receive:

- 2 mg VEGF Trap-Eye PRN in a 50 μL injection volume from a PFS (Sealed, sterile 3 mL Vials of approximately 0.5 mL of VEGF Trap-Eye. The VEGF Trap-Eye was withdrawn into a 1 mL syringe using aseptic technique. A sterile 30-gauge needle was used for intravitreal injection).
- 2 mg VEGF Trap-Eye PRN in a 50 μL injection volume from a Vial (Single-use, PFS glass syringes with Snap-off Tip Cap. A plastic plunger rod was attached to the rubber stopper inside the barrel of the syringe. After removing the syringe cap, a 30-gauge needle was attached for administration).

Each subject had only 1 eye that was designated as the study eye and was treated in 1 of the 2 treatment arms after enrollment. The other eye was designated as the fellow (non-study) eye and treated if the investigator deemed necessary. Subjects were scheduled to return to the clinical site every 8 weeks. At each visit, the investigator determined the need for IVT injection based on his/her assessment of the subject. If, at any point during the study, in the investigator's opinion, a subject required dosing or evaluation more frequently than every 8 weeks, monthly visits and dosing were permitted. The maximum frequency for injection in the study eye was every 4 weeks. Injection for the fellow eye could be given no less frequently than 6 or 7 days after an injection in the study eye. The fellow eye received the same dose of VEGF Trap-Eye as the study eye. The current result analysis is based on a data cut-off date of 6/28/10. The duration of this study was approximately 39 months. This included 38 months of treatment and 1 month of follow-up (Figure 1). The study is ongoing but not recruiting. Since subjects were randomized upon completion of dosing in their previous study, they were in the current study for varying amounts of time.

Inclusion Criteria:

Subjects' Study Eye:

- Read (if unable to read due to visual impairment, read verbatim by the person administering the informed consent or a family member) understood, and signed the ICF
- Prior participation in 1 of the following studies:
    - VGFT-OD-0502 open-label extension, completing the final/termination visit
    - VGFT-OD-0508, completing visit 16 (week 52)
    - VGFT-OD-0603, completing visit 26 (week 52)
- Willingness to comply with study drug and evaluation procedures
- Willing, committed, and able to return for all clinic visits and complete all study-related procedures

Subjects' Fellow Eye (Not Previously Enrolled):

- CNV secondary to AMD that now required treatment, or prior treatment in the fellow eye with VEGF Trap-Eye in VGFT-OD-0502, VGFT-OD-0508, or VGFT-OD-0603.

Exclusion Criteria:

Subjects' Study Eye：

- Any ocular or systemic adverse events (AEs) during prior study participation that in the investigator's opinion precluded continued intravitreal injection with VEGF Trap-Eye
- Presence of any condition, which, in the investigator's opinion, jeopardized the subject's participation in the study

Subjects' Fellow Eye (Not Previously Enrolled):

- Prior treatment with the following:
    - Besides VEGF Trap-Eye, any prior pegaptanib sodium, bevacizumab, ranibizumab, or other anti-VEGF agent
    - Extrafoveal laser coagulation treatment within 8 weeks of the first dose of VEGF Trap-Eye
    - PDT or IVT administration of triamcinolone acetonide or other steroids within 8 weeks of the first dose of VEGF Trap-Eye
    - Juxtascleral steroids or anecortave acetate within 180 days (6 months) of the first dose of VEGF Trap-Eye
- History of submacular surgery or any surgical AMD interventions
- Any ocular treatment for AMD within 30 days of the first dose of VEGF Trap-Eye
- History of surgery for retinal disease, including (but not limited to), retinal detachment, epiretinal membrane, and pars plana vitrectomy
- Any ocular surgery within 12 weeks of the first dose of VEGF Trap-Eye
- History of vitreous hemorrhage within 4 weeks of the first dose of VEGF Trap-Eye
- Presence of pigment epithelial tears or rips
- Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8.0 diopters or more, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis
- Active ocular infection
- Active ocular inflammation (grade trace or above)
- History or clinical evidence of diabetic retinopathy, diabetic macular edema, or any retinal vascular disease other than CNV
- History of corneal transplant or corneal dystrophy

- History of idiopathic or autoimmune associated uveitis
- Uncontrolled glaucoma, in the investigator's judgment
- History of macular hole of stage 3 and above
- Aphakia or pseudophakia with the absence of a posterior capsule (unless it occurred as a result of a yttrium aluminum garnet capsulotomy)

Study Schedule VGFT-OD-0702

WEEK	Enrollment[a]	Wk 8	Wk 16	Wk 24	Wk 32	Wk 40	Wk 48	Wk 56	Wk 64	Wk 72	Wk 80	Wk 88	Wk 96	Wk 104	Wk 112	Wk 120	Wk 128	Wk 136	Wk 144	Wk 152	Wk 156/ET
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Sign Informed Consent[b]	X																				
Randomization[c]	X																				
Medical/Ophthalmic History	X																				
Vital Signs (Temperature, BP, Pulse)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Interval History (AEs & Con Meds)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect Ophthalmic/Slit Lamp	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP[e]	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X
Prot Refraction/VA (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology & Chemistry Panel[f]	X[f]			X[f]			X[f]			X[f]			X[f]			X[f]			X[f]		X[f]
Urinalysis	X[f]			X[f]			X[f]			X[f]			X[f]			X[f]			X[f]		X[f]
Serum for antibody[f]	X[f]			X[f]			X[f]			X[f]			X[f]			X[f]			X[f]		X[f]
VEGF Trap-Eye Injection[g,h,i]	O[g,k]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	
Telephone Safety Check (3 ±1 day)[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

BP = blood pressure; AE = adverse event; Con Meds = concomitant medications; VA = visual acuity; IOP = intraocular pressure; ETDRS = Early Treatment Diabetic Retinopathy Study; VEGF = vascular endothelial growth factor

a Enrollment occurred the same day as the completion visit for the original protocol the subject was enrolled but no later than 8 weeks (visit 2) from that date. Exit procedures for the original protocol were used as baseline for this protocol. If enrollment occurred 8 weeks from date of completion of the original study, these assessments and procedures were completed after signed informed consent.

b Informed consent was signed prior to completion of exit procedures for the original protocol.

c Randomization occurred at the subject's visit immediately following implementation of amendment 1

d AEs were recorded from the time informed consent was signed until study completion. If a subject withdrew, AEs were recorded until withdrawal or 30 days after last dose of study drug, whichever was later.

e Measure IOP pre-injection and 30-60 minutes post-injection

f Draw sample prior to administration of study drug

g Subject was assessed as to whether IVT injection was required at scheduled 8 week and optional monthly visits. O = Optional

h See Appendix C of the study protocol, in Appendix 1.1 for study drug injection procedures

i Minimum required assessment for dosing was every 8weeks. Dosing could occur more frequently (every 4 weeks) at the investigator's discretion. Refer to Appendix B (optional visits) of the study protocol in Appendix 1.1 for required procedures.

j Mandatory telephone safety checks 3 ± 1 days post-injection

k The fellow eye could be treated at the enrollment visit only if the study eye was not dosed at the same visit.

Study Schedule VGFT-OD-0702 for Optional Visits

WEEK	STUDY EYE Weeks 4, 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, and 148	FELLOW EYE Weeks 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 97, 101, 105, 109, 113, 117, 121, 125, 129, 133, 137, 141, 145, 149, and 153 (6 or 7 days post-injection)
Sign Informed Consent		
Medical/Ophthalmic History		
Physical Examination		
Vital Signs (temperature, blood pressure, and pulse)	X	
Interval History (AEs & Con Meds)[c]	X	X
Indirect Ophthalmic/Slit Lamp	X	X
IOP[d]	X[d]	X[d]
Prot Refraction/VA (ETDRS)	X	X
Hematology & Chemistry Panel[e]		
Urinalysis[e]		
Serum for antibody[e]		
VEGF Trap-Eye Injection[f,g,h]	O[f]	O
Telephone Safety Check (3 ±1 day)[i]	X	X

AE = adverse event; Con Meds = concomitant medications; VA = visual acuity; IOP = intraocular pressure; ETDRS = Early Treatment Diabetic Retinopathy Study; VEGF = vascular endothelial growth factor

c AEs were recorded from the time informed consent was signed until study completion. If a subject withdrew, AEs were recorded until withdrawal or 30 days after last dose of study drug, whichever was later.

d Measure IOP pre-injection and 30-60 minutes post-injection

e Draw sample prior to administration of study drug

f Subject was assessed as to whether IVT injection was required at scheduled 8-week and optional monthly visits. O = Optional

g See Appendix C of the study protocol in Appendix 1.1 for study drug injection procedures

h Minimum required assessment for dosing was every 8 weeks. Dosing could occur more frequently (every 4 weeks) at the investigator's discretion. Refer to Appendix B (optional visits) of the study protocol, in Appendix 1.1 for required procedures.

i Mandatory telephone safety checks 3 ± 1 days post-injection

Review of Efficacy

Demographics

VIEW #1: Full Analysis Set

	0.5RQ4 N=304	**2Q4 N=304**	**0.5Q4 N=301**	**2Q8 N=301**
Age				
Mean (sd)	78.2 (7.6)	77.7 (7.9)	78.4 (8.1)	77.9 (8.4)
Range	56-99	51-94	50-94	49-94
Gender				
Female	172	194	167	178
Male	132	110	134	123
Race				
White	296	295	291	287
African American	1	1	0	1
Asian	0	3	5	4
American Indian	2	0	2	1
Native Hawaiian	1	0	0	1
Not reported	4	5	3	6
Multiple	0	0	0	1
Ethnicity				
Non-Hispanic	297	293	290	289
Hispanic	7	11	11	12
Eye color				
Dark	101	107	106	99
Other	203	195	194	201
Missing	0	2	1	1

VIEW #2: Full Analysis Set

	0.5RQ4 N=291	**2Q4 N=309**	**0.5Q4 N=296**	**2Q8 N=306**
Age				
Mean (sd)	73.0 (9.0)	74.1 (8.5)	74.7 (8.6)	73.8 (8.6)
Range	50-92	50-93	51-93	50-93
Gender				
Female	169	176	147	175
Male	122	133	149	131
Race				
White	213	226	219	217
African American	1	0	1	2
Asian	60	67	61	69
Missing	17	16	15	18
Ethnicity				
Non-Hispanic	239	259	241	251
Hispanic	52	50	55	55
Eye color				

	0.5RQ4 N=291	2Q4 N=309	0.5Q4 N=296	2Q8 N=306
Dark	177	117	176	193
Other	114	132	120	113

VIEW #1: Baseline Disease Characteristics (Full Analysis Set)

	RQ4 N=304	2Q4 N=304	0.5Q4 N=301	2Q8 N=301
Mean Visual Acuity Letter Score	54.0 (13.4)	55.2 (13.2)	55.6 (13.1)	55.7 (12.8)
Mean Retinal Thickness (microns)	266.8	261.8	266.7	269.0
Area of CNV (mm squared)	6.5	6.6	6.5	6.6
Lesion Type				
Occult	115	110	121	118
Min. classic	101	105	97	110
Predom. classic	82	87	81	71
Total Lesion Size	6.99	6.98	6.95	6.98

VIEW #2: Baseline Disease Characteristics (Full Analysis Set)

	RQ4 N=291	2Q4 N=309	0.5Q4 N=296	2Q8 N=306
Mean Visual Acuity Letter Score	53.8 (13.5)	52.8 (13.9)	51.6 (14.2)	52.4 (13.9)
Mean Retinal Thickness (microns)	325.9	334.6	326.5	342.6
Mean area of CNV (mm squared)	7.59	8.25	7.7	7.8
Lesion Type				
Occult	116	123	113	110
Min. classic	104	112	103	106
Predom. classic	70	72	80	88
Mean Total Lesion Size	8.01	8.72	8.17	8.22

Safety analysis set (SAF): All subjects who received any study drug.

Full analysis set (FAS): All randomized subjects who received any study drug and had a Baseline and at least one post-Baseline BCVA assessment.

Per protocol set (PPS): All subjects in the FAS who received at least 9 injections of study drug or sham and attended at least 9 scheduled visits during the first year, except for those who were excluded because of major protocol violations. A major protocol violation is one that may affect the interpretation of study results (ie. missing two consecutive injections before administration of the 9th injection). Sham injections were counted as doses administered for the purpose of defining the PPS. The PPS also included subjects without major protocol deviations who discontinued due to treatment failure at anytime during the first 52 weeks of the study. A treatment failure is a subject who had a decrease from Baseline in BCVA of at least 15 letters at two consecutive assessments, 4 weeks apart, during the first 52 weeks of the study.

For measures that were proportions of responders (ie. vision gainers or vision maintainers), the last observation carried forward (LOCF) approach was used to impute missing data for all efficacy variables. Baseline values were not carried forward. Subjects who were not treatment failures and withdrew prior to Week 36 were not included in the primary efficacy analysis (not in PPS), but were included in the secondary efficacy analysis (in FAS). The PPS was used for primary analysis (statistical evaluation of non-inferiority). For completeness, confidence intervals were also constructed using the FAS. The FAS was used for all hypothesis tests of

superiority. Analyses of superiority using the PPS were also done for supportive analyses. Safety analyses were performed in the SAF.

VIEW 1: Analysis Population

	RQ4	2Q4	0.5Q4	2Q8
Randomized	306	304	304	303
Safety set (SAF)	304	304	304	303
Full analysis set (FAS)	304	304	301	301
Per protocol set (PP)	269	285	270	265

VIEW 2: Analysis Population

	RQ4	2Q4	0.5Q4	2Q8
Randomized	303	313	311	313
Safety set (SAF)	291	309	297	307
Full analysis set (FAS)	291	309	296	306
Per protocol set (PP)	269	274	268	270

Study VGFT-OD-0702: Demographics (All Randomized Set)

	Vial N=50	PFS N=99
Sex		
Male	21	35
Female	29	64
Ethnicity		
Hispanic	1	3
Not Hispanic	49	96
Race		
White	49	99
African American	0	0
American Indian	1	0
Age		
Mean (sd)	79.2 (7.9)	77.0 (8.3)
Min-Max	59-93	55-93

Study VGFT-OD-0702: Disposition

	Vials	PFS	Total
Enrolled			157
Randomized	50	99	149
Study eye treated	43	87	130

Primary Efficacy Endpoint

The primary analysis is an evaluation of the non-inferiority of VEGF Trap-Eye to ranibizumab and includes the following conditional sequence of calculations of the confidence intervals for the difference between treatments in proportion of subjects maintaining vision at Week 52:

Comparison 1: VEGF Trap-Eye 2mg q4 weeks versus ranibizumab
Comparison 2: VEGF Trap-Eye 0.5mg q4 weeks versus ranibizumab
Comparison 3: VEGF Trap-Eye 2mg q8 weeks versus ranibizumab

The non-inferiority margin in individual VIEW 1 and VIEW 2 studies was 10%. The primary analysis was a conditional sequence (a priori ordered hypotheses) of statistical evaluation of non-inferiority of VEGF Trap-Eye to 0.5 mg ranibizumab. VEGF Trap-Eye was to be considered non-inferior to ranibizumab if the confidence interval of the difference lay entirely below 10%, where a positive difference favors ranibizumab. These analyses were based on the PPS at Week 52. Once the non-inferiority was demonstrated, the superiority of VEGF Trap-Eye to ranibizumab was examined.

VIEW #1: Primary Efficacy Analysis (FAS Population with LOCF)

	RQ4 N=304	**2Q4 N=304**	**0.5Q4 N=301**	**2Q8 N=301**
Subjects With Maintained vision at Week 52	285 (93.8%)	289 (95.1%)	286 (95.0%)	284 (94.4%)
Difference (%) (95.1% CI)		-1.3 (-5.0; 2.4)	-1.3 (-4.9; 2.4)	-0.6 (-4.4; 3.2)

VIEW #1: Primary Efficacy Analysis (PP Population with observed cases)

	RQ4 N=269	**2Q4 N=285**	**0.5Q4 N=270**	**2Q8 N=265**
Subjects With Maintained vision at Week 52	243 (94.9%)	260 (94.9%)	241 (96.4%)	237 (96.3%)
Difference (%) (95.1% CI)		0.0 (-3.7, 3.8)	-1.5 (-5.0, 2.1)	-1.4 (-5.0, 2.2)

VIEW #2: Primary Efficacy Analysis (FAS Population with LOCF)

	RQ4 N=291	**2Q4 N=309**	**0.5Q4 N=296**	**2Q8 N=306**
Subjects With Maintained vision at Week 52	276 (94.9%)	292 (94.5%)	282 (95.3%)	292 (95.4%)
Difference (%) (95.1% CI)		0.4 (-3.3, 4.0)	--0.4 (-4.0, 3.1)	--0.6 (-4.1, 2.9)

VIEW #2: Primary Efficacy Analysis (PP Population with observed cases)

	RQ4 N=261	**2Q4 N=263**	**0.5Q4 N=257**	**2Q8 N=264**
Subjects With Maintained vision at Week 52	246 (94.3%)	251 (95.4%)	248 (96.5%)	253 (95.8%)
Difference (%) (95.1% CI)		-1.18 (-4.99, 2.62)	-2.25 (-5.87, 1.38)	-1.58 (-5.31, 2.15)

In Study VIEW #2, the applicant did not adjust the CI to 95.1% for the interim safety look. The Agency did re-adjust the analysis to include a statistical adjustment as shown in the above tables.

Both studies met their primary endpoint. When compared to ranibizumab all 3 doses of VEGF Trap-Eye were non-inferior when comparing the proportion of subjects who maintained vision (lost less than 15 letters lost in the ETDRS letter score). However, none of the doses were superior to ranibizumab.

Various sensitivity analyses were conducted to examine the robustness of the primary efficacy analysis results. These sensitivity analyses used different statistical methods or different methods to handle missing values, including using the observed values, the worst observation carried forward method, counting all drop-outs and treatment failures as non-responders, and multiple imputation methods. The results of these sensitivity analyses are similar to those of the primary analysis.

Analysis of Secondary Endpoints

If all three VEGF Trap-Eye groups were shown to be non-inferior to ranibizumab on the primary endpoint, additional comparisons of VEGF Trap-Eye groups to ranibizumab were made with respect to secondary endpoints. The secondary efficacy analysis was conducted in the FAS population and was to test for superiority of VEGF Trap-Eye over ranibizumab. A conditional sequence of statistical hypotheses (a-priori ordered hypotheses) was to control for multiplicity for secondary endpoint analyses. The following sequence of analyses was performed:

1. VEGF Trap-Eye 2Q4 was compared to ranibizumab relative to subjects' mean change in BCVA as measured by ETDRS letter score from Baseline to Week 52.
2. VEGF Trap-Eye 2Q4 was compared to ranibizumab relative to the proportions of subjects who gained 15 or more letters of vision from Baseline to Week 52.
3. VEGF Trap-Eye 2Q4 was compared to ranibizumab relative to subjects' mean change in total NEI-VFQ-25 score from Baseline to Week 52.
4. VEGF Trap-Eye 0.5Q4 was compared to ranibizumab relative to subjects' mean change in BCVA as measured by ETDRS letter score from Baseline to Week 52.
5. VEGF Trap-Eye 0.5Q4 was compared to ranibizumab relative to the proportions of subjects who gained 15 or more letters of vision from Baseline to Week 52.
6. VEGF Trap-Eye 0.5Q4 was compared to ranibizumab relative to subjects' mean change in total NEI-VFQ-25 score from Baseline to Week 52.
7. VEGF Trap-Eye 2Q8 was compared to ranibizumab relative to subjects' mean change in BCVA as measured by ETDRS letter score from Baseline to Week 52.
8. VEGF Trap-Eye 2Q8 was compared to ranibizumab relative to the proportions of subjects who gained 15 or more letters of vision from Baseline to Week 52.
9. VEGF Trap-Eye 2Q8 was compared to ranibizumab relative to subjects' mean change in total NEI-VFQ-25 score from Baseline to Week 52.
10. VEGF Trap-Eye 2Q4 was compared to ranibizumab relative to subjects' mean change in CNV area from Baseline to Week 52.
11. VEGF Trap-Eye 0.5Q4 was compared to ranibizumab relative to subjects' mean change in CNV area from Baseline to Week 52.
12. VEGF Trap-Eye 2Q8 was compared to ranibizumab relative to subjects' mean change in CNV area from Baseline to Week 52.

VIEW #1: Mean Change from Baseline to Week 52 in ETDRS Letter Score in the Study Eye (Full Analysis Set with LOCF)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=301**	**2Q8 N=301**
Baseline				
Mean ETDRS letter score(sd)	54.0 (13.4)	55.2 (13.2)	55.6 (13.1)	55.7 (12.8)
Week 52				
Mean ETDRS letter score (sd)	62.1 (17.7)	66.1 (16.2)	62.4 (16.5)	63.6 (16.9)
Week 52 (Mean change from baseline)	8.1 (15.3)	10.9 (13.8)	6.9 (13.4)	7.9 (15.0)

VIEW #2: Mean Change from Baseline to Week 52 in ETDRS Letter Score in the Study Eye (Full Analysis Set with LOCF)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=296**	**2Q8 N=306**
Baseline				
Mean ETDRS letter score (sd)	53.8 (13.5)	52.8 (13.9)	51.6 (14.2)	51.6 (13.9)
Week 52				
Mean ETDRS letter score (sd)	63.1 (16.6)	60.4 (18.3)	61.3 (17.8)	60.5 (17.5)
Week 52 (Mean change from baseline)	9.4 (13.5)	7.6 (12.6)	9.7 (14.1)	8.9 (14.4)

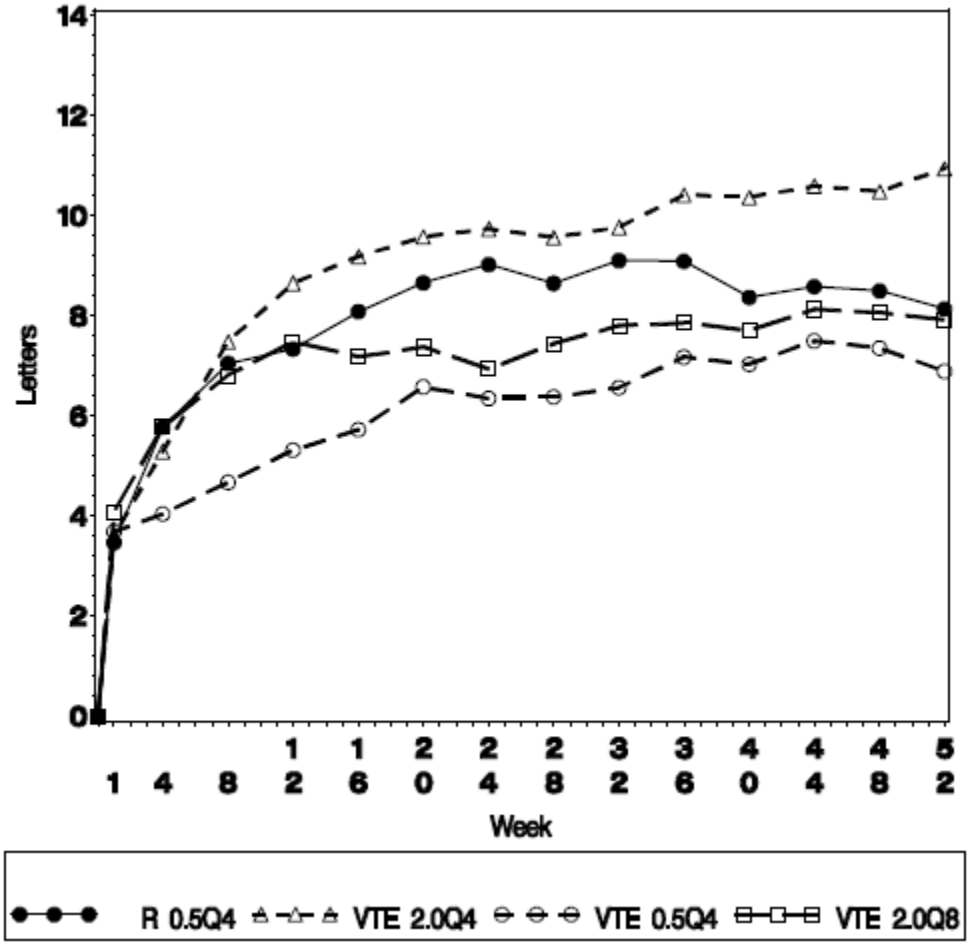
VIEW #1: Mean ETDRS Letter Score (Full analysis Set with LOCF)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=301	2Q8 N=301
Screening	55.2	56.9	56.1	56.8
Baseline	54.0	55.2	55.6	55.7
Week 1	57.4	58.8	59.4	59.8
Week 4	59.7	60.5	59.6	61.5
Week 8	61.0	62.7	60.2	62.5
Week 12	61.3	63.8	60.9	63.2
Week 16	62.0	64.4	61.3	62.9
Week 20	62.6	64.7	62.1	63.1
Week 24	63.0	64.9	61.9	62.6
Week 28	62.6	64.7	61.9	63.1
Week 32	63.1	64.9	62.1	63.5
Week 36	63.0	65.6	62.7	63.5
Week 40	62.3	65.5	62.6	63.4
Week 44	62.5	65.8	63.0	63.8
Week 48	62.5	65.7	62.9	63.7
Week 52	62.1	66.1	62.4	63.6

VIEW #1: Mean Change in ETDRS Letter Score from Baseline (Full analysis Set with LOCF)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=301	2Q8 N=301
Week 1	3.5	3.6	3.7	4.1
Week 4	5.8	5.3	4.0	5.8
Week 8	7.0	7.5	4.7	6.8
Week 12	7.3	8.7	5.3	7.5
Week 16	8.1	9.2	5.7	7.2
Week 20	8.7	9.6	6.6	7.4
Week 24	9.0	9.7	6.3	6.9
Week 28	8.7	9.6	6.4	7.4
Week 32	9.1	9.8	6.6	7.8
Week 36	9.1	10.4	7.2	7.9
Week 40	8.4	10.4	7.0	7.7
Week 44	8.6	10.6	7.5	8.1
Week 48	8.5	10.5	7.4	8.1
Week 52	8.1	10.9	6.9	7.9

VIEW #1: Mean Change from Baseline in Visual Acuity Through Week 52 by Treatment Group (Full Analysis Set with LOCF)



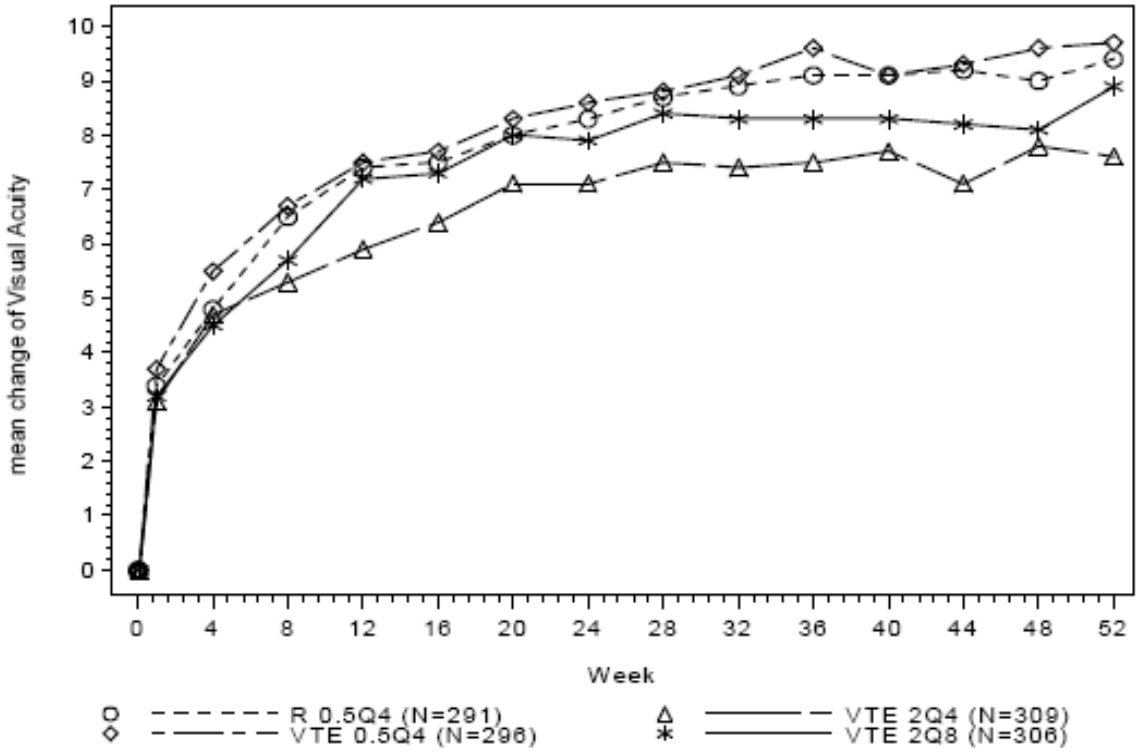
VIEW #2: Mean ETDRS Letter Score (Full analysis Set with LOCF)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=296**	**2Q8 N=306**
Screening	55.0	53.6	52.5	52.1
Baseline	53.8	52.8	51.6	51.6
Week 1	57.2	55.8	55.3	54.8
Week 4	58.6	57.4	57.1	56.1
Week 8	60.2	58.1	58.3	57.3
Week 12	61.2	58.7	59.1	58.7
Week 16	61.3	59.2	59.3	58.9
Week 20	61.8	59.9	59.9	59.6
Week 24	62.1	59.9	60.2	59.5
Week 28	62.5	60.2	60.4	60.0
Week 32	62.6	60.2	60.7	59.9
Week 36	62.9	60.2	61.2	59.9
Week 40	62.8	60.5	60.7	59.9
Week 44	63.0	59.9	60.9	59.8
Week 48	62.7	60.6	61.2	59.7
Week 52	63.1	60.4	61.3	60.5

VIEW #2: Mean Change in ETDRS Letter Score from Baseline (Full analysis Set with LOCF)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=296**	**2Q8 N=306**
Week 1	3.4	3.1	3.7	3.2
Week 4	4.8	4.7	5.5	4.5
Week 8	6.5	5.3	6.7	5.7
Week 12	7.4	5.9	7.5	7.2
Week 16	7.5	6.4	7.7	7.3
Week 20	8.0	7.1	8.3	8.0
Week 24	8.3	7.1	8.6	7.9
Week 28	8.7	7.5	8.8	8.4
Week 32	8.9	7.4	9.1	8.3
Week 36	9.1	7.5	9.6	8.3
Week 40	9.1	7.7	9.1	8.3
Week 44	9.2	7.1	9.3	8.2
Week 48	9.0	7.8	9.6	8.1
Week 52	9.4	7.6	9.7	8.9

VIEW #2: Mean Change from Baseline in Visual Acuity Through Week 52 by Treatment Group (Full Analysis Set with LOCF)



VGFT-OD-0702: Mean ETDRS Letter Score (Full Analysis Set with LOCF) Cut Off Date 6/28/2010

	Vial N=45	**PFS N=87**
Baseline	60.2	62.4
Week 8	59.3	62.6
Week 16	60.6	61.7
Week 24	59.9	61.1
Week 32	59.6	60.6
Week 40	60.0	60.6
Week 48	59.1	60.6
Week 56	58.9	60.5
Week 64	58.2	58.8
Week 72	57.1	59.5
Week 80	57.6	59.7
Week 88	56.6	59.6
Week 96	56.8	58.1
Week 104	56.3	58.6
Week 112	56.1	58.6
Week 120	55.2	58.7
Week 128	55.2	58.4
Week 136	55.7	58.3
Week 144	55.6	58.3
Week 152	55.6	58.3
Week 156	55.6	58.3

Review of Safety

Data Pools for Safety Evaluation for AMD Indication

Study	Phase	Number of Patients	Status
VGFT-OD-0603	1	20	Completed
VGFT-OD-0502	1	51	Completed
VGFT-OD-0702	Phase 1/Phase 2 extension	157	Active but not recruiting
VGFT-OD-0508	2	157	Completed
VIEW 1 (VEGF-OD-0605)	3	1215	Ongoing
VIEW 2 (311523)	3	1204	Ongoing
VGFT-OD-0910	3 extension	222	Ongoing
TOTAL		**2230**	

The above studies were the studies with aflibercept in patients with AMD. Aflibercept has also been studied in patients with DME, CRVO, and oncology indications.

Overall Exposure

VIEW #1: Treatment Exposure During the First Year (Safety Analysis Set)

	RQ4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Number of Injections During the First Year Including Sham				
1-4	9	1	11	6
5-8	9	6	5	17
9-13	286	297	288	280
Mean (sd)	12.1 (2)	12.5 (1)	12.1 (2)	12.0 (2)
Mean Number of Injections During the First Year Excluding Sham	12.1 (2)	12.5 (1)	12.1 (2)	7.5 (1)
Total Amount of Study Medication During the First Year (mg)				
Mean (sd)	6.0 (1)	24.9 (2)	6.0 (1)	14.9 (2)
Min-Max	1-7	6-26	1-7	2-16

VIEW #2: Treatment Exposure During the First Year (Safety Analysis Set)

	RQ4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Number of Injections During the First Year Including Sham				
1-4	5	10	9	9
5-8	6	12	8	11
9-13	280	287	280	287
Mean (sd)	12.7 (1.1)	12.6 (1.3)	12.7 (1.2)	12.6 (1.3)
Mean Number of Injections During the First Year Excluding Sham	12.7 (1.1)	12.6 (1.3)	12.6 (1.2)	7.7 (0.8)
Total Amount of Study Medication During the First Year (mg)				
Mean (sd)	6.2 (0.90)	24.4 (4.37)	6.2 (1.03)	15.1 (2.88)
Min-Max	0.5-8.0	2.0-28.0	0.5-8.0	2.0-34.0

Study VGFT-OD-0702: Treatment Exposure During the First Year (All Randomized Population)

	Vial N=50	PFS N=99
Number of Injections		
Mean (sd)	5.8 (4.8)	6.2 (5.2)
Min-Max	0-22	0-23
Total Amount of Study Medication (mg)		
Mean (sd)	11.6 (9.6)	12.4 (10.4)
Min,Max	0-44	0-46

Study VGFT-OD-0702: Treatment Duration (Days) in the First Year (Safety Analysis Set)

	Vial N=50	PFS N=99
Duration of Study Medication (Weeks)		
Mean (sd)	72.8 (47.1)	72.9 (46.8)
Min-Max	0-139	0-140

Deaths

VIEW #1: Listing of Deaths (Safety Analysis Set)

Subject Number	Treatment Group	Study Day	Number of Days After Last Dose	Cause
145-022	RQ4	19	19	Myocardial infarction
502-001	RQ4	223	83	Hepatic neoplasm
502-008	RQ4	259	35	Lung neoplasm
506-011	RQ4	259	77	CHF
507-019	RQ4	368	33	Aspiration pneumonia
142-027	2Q4	206	15	COPD
314-002	2Q4		54	Respiratory insufficiency
218-008	0.5Q4	99	13	Cerebral hemorrhage
502-003	0.5Q4	80	53	Myocardial infarction
114-018	2Q8	144	4	Hemorrhagic shock
146-016	2Q8	211	15	CVA
182-002	2Q8	313	33	Myocardial infarction
237-003	2Q8	171	31	Arteriosclerosis
284-002	2Q8	113	29	CHF
305-006	2Q8	150	31	Leukemia
309-009	2Q8	233	9	COPD
505-004	2Q8	257	56	CHF

VIEW #2: Listing of Deaths (Safety Analysis Set)

Subject Number	Treatment Group	Study Day	Number of Days After Last Dose	Cause
160020002	RQ4	unknown	unknown	Esophageal CA
440030022	RQ4	118	3	Acute MI
240090004	0.5Q4	unknown	unknown	unknown
760010013	0.5Q4	46	18	MI
100220010	2Q4	90	35	CVA
600090017	2Q4	359	77	Pyrexia*
600130001	2Q4	251	58	Cardiopulmonary failure
430060004	2Q8	196	27	Lung CA
600040008	2Q8	60	4	Cardiac arrest

**This patient had experienced a road traffic accident causing polytrauma a few weeks before fatal pyrexia.*

Study VGFT-OD-0702: Listing of Deaths

Subject Number	Number of Days After Last Dose	Cause
001-0112	43	Unknown at this time
015-1501	216	Stroke
018-1801	88	Lung CA
020-2007	159	Lung CA
027-2709	N/A	Myocardial infarction
028-2806	N/A	Respiratory failure
044-4401	106	Pulmonary edema
005-0504	564	Lung CA

Nonfatal Serious Adverse Events

VIEW #1: Ocular Treatment Emergent SAEs in the Study Eye (Safety Analysis Set)

	RQ4 N=304	**2Q4 N=304**	**0.5Q4 N=304**	**2Q8 N=303**
Number of Subjects With At Least 1 Ocular SAE in Study Eye	10 (3.3%)	7 (2.3%)	6 (2.0%)	3 (1.0%)
Endophthalmitis	3	3	0	0
Reduced Visual Acuity	2	1	2	0
Retinal hemorrhage	2	0	0	2
Angle closure glaucoma	0	1	0	0
Cataract	0	0	1	0
Keratitis	0	1	0	0
Macular hole	0	0	1	0
Retinal degeneration	0	1	0	0
Retinal edema	1	0	1	0
RPE tear	0	0	0	1
Retinal tear	1	0	1	0
Incorrect dose administered	1	0	0	0
IOP increased	1	0	0	0

VIEW #1: Non-Ocular Treatment SAEs (Safety Analysis Set)

	RQ4 N=304	**2Q4 N=304**	**0.5Q4 N=304**	**2Q8 N=303**
Number of Subjects With At Least 1 Non-ocular SAE	57 (18.8%)	40 (13.2%)	50 (16.4%)	51 (16.8%)
Infections	15	6	11	12
Pneumonia	7	3	2	5
Bronchitis	0	0	1	1
Cellulitis	2	1	1	0
Gastroenteritis	1	0	0	2
UTI	1	2	0	0
Bacterial arthritis	0	0	0	1
Clostridial infection	0	0	0	1
C. diff colitis	0	0	1	0
Endocarditis	0	0	0	1
Escherichia UTI	1	0	1	0
Lobar pneumonia	0	0	0	1
Pyelonepritis	0	1	0	0
Septic shock	0	0	0	1
Sinusitis	0	0	1	0
Fungal sinusitis	0	0	1	0
Staph bacteremia	0	0	0	1
Bacterial UTI	0	0	1	0
Vestibular neuronitis	0	0	1	0
Viral infection	0	0	1	0
Device related infection	1	0	0	0
Diverticulitis	1	0	0	0
Lung infection	1	0	0	0
Pharyngitis	1	0	0	0
Scrotal abscess	1	0	0	0
Viral pericarditis	1	0	0	0

	RQ4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Cardiac Disorders	14	7	10	11
A fib	2	2	0	3
CHF	2	1	2	3
Myocardial infarction	3	1	3	2
CAD	4	0	4	0
Acute myocardial infarction	0	1	1	0
Acute coronary syndrome	0	1	0	0
Aortic valve stenosis	0	0	0	1
Arrhythmia	0	1	0	0
Bradycardia	1	0	1	0
Cardiac arrest	0	0	1	0
Coronary artery occlusion	1	1	0	0
Intracardiac thrombus	0	0	0	1
Mitral valve incompetence	0	0	1	0
Sick sinus syndrome	0	0	0	1
Tachycardia	0	0	0	1
Ventricular tachycardia	0	0	1	0
Unstable angina	1	0	0	0
Chronic cardiac failure	1	0	0	0
Supraventricular tachycardia	1	0	0	0
Neoplasms	10	9	10	9
Squamous cell of skin	3	2	1	3
Bladder transitional cell	0	1	1	0
Breast CA	0	0	2	0
Prostate CA	1	0	2	0
Prostate metastatic	0	1	0	1
Breast CA in situ	0	0	1	0
Bronchioalveolar CA	0	1	0	0
CLL	0	1	0	0
Colon CA	0	1	0	0
Leukemia	0	0	0	1
Lung	0	1	0	0
Malignant melanoma	1	0	1	0
Non-small cell lung CA	0	0	1	0
Rectosigmoid CA	0	0	0	1
Renal cell CA	0	0	0	1
Salivary gland CA	0	0	1	0
Thyroid CA	0	0	0	1
Tonsil CA	0	1	0	0
Transitional cell CA	0	0	0	1
Atypical fibroxanthoma	1	0	0	0
Hepatic neoplasm	1	0	0	0
Lung neoplasm malignant	1	0	0	0
Esophageal CA	1	0	0	0
Tumor perforation	1	0	0	0
Nervous system disorders	1	6	13	6
TIA	0	2	5	1
CVA	0	0	1	3
Syncope	1	1	2	0
Carotid artery stenosis	0	2	0	0
Subarachnoid hemorrhage	0	0	1	1
Balance disorder	0	0	0	1
Cerebral artery thrombosis	0	1	0	0

	RQ4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Cerebral hemorrhage	0	0	1	0
Cerebral infarction	0	0	1	0
Ischemic cerebral infarction	0	1	0	0
Metabolic encephalopathy	0	0	1	0
Spinal cord compression	0	0	1	0
Injury and poisoning	5	6	5	6
Fall	5	6	4	6
Hip fracture	1	2	2	0
Subdural hematoma	1	0	1	2
Humerous fracture	0	1	1	0
Rib fracture	0	0	1	1
Femur fracture	0	1	0	0
Incisional hernia	0	0	0	1
Pubis fracture	1	1	0	0
Snake bite	0	0	0	1
Subcutaneous hematoma	0	0	0	1
Traumatic brain injury	0	1	0	0
Upper limb fracture	0	0	0	1
Lumbar vertebral fracture	1	0	0	0
Spinal fracture	1	0	0	0
GI disorders	5	4	4	3
Gastritis	0	1	0	1
Ischemic colitis	0	0	1	0
Constipation	0	0	1	0
Diarrhea	0	0	1	0
Duodenal ulcer	1	0	1	0
GI motility disorder	0	0	1	0
GERD	0	1	0	0
Hematochezia	0	1	0	0
Hiatus hernia	0	0	0	1
Ileus	0	1	0	0
Lower GI bleed	0	0	0	1
Colonic polyp	1	0	0	0
Erosive gastritis	1	0	0	0
Hemorrhoids	1	0	0	0
Intestinal obstruction	1	0	0	0
Respiratory disorders	4	4	3	4
COPD	2	3	2	2
Pneumonitis	0	1	0	1
Pleural effusion	0	1	0	0
Aspiration pneumonia	1	0	0	1
Pulmonary embolism	0	0	1	0
Pulmonary fibrosis	0	1	0	0
Respiratory failure	0	0	0	1
Apnea attack	1	0	0	0
Metabolism disorder	2	3	3	3
Hyponatremia	1	1	1	1
Dehydration	0	0	1	1
DM	0	0	1	0
Inadequate control DM	0	0	0	1
Hyperkalemia	0	0	1	0

	RQ4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Hypokalemia	1	1	0	0
Malnutrition	0	1	0	0
Hypoglycemic shock	0	1	0	0
Vascular disorders	5	2	3	4
DVT	0	0	1	1
Aortic aneurysm	1	1	0	0
Aortic stenosis	0	0	0	1
Arteriosclerosis	0	0	0	1
HTN	2	0	1	0
Iliac artery occlusion	0	0	1	0
Peripheral artery occlusion	0	1	0	0
Hemorrhagic shock	0	0	0	1
Aortic aneurysm rupture	1	0	0	0
Orthostatic hypotension	1	0	0	0
General disorders	1	2	2	2
Asthenia	0	0	1	0
Catheter site hematoma	0	0	0	1
Chest pain	1	1	0	0
Drug withdrawal syndrome	0	0	1	0
Non-cardiac chest pain	0	1	0	0
Pyrexia	0	0	0	1
Musculoskeletal disorders	5	1	0	3
Back pain	0	0	0	1
Intervertebral disc degeneration	0	0	0	1
Intervertebral disc protrusion	0	1	0	0
Lumbar spinal stenosis	1	0	0	1
Osteoarthritis	3	0	0	0
Spinal column stenosis	1	0	0	0
Spinal osteoarthritis	1	0	0	0
Spondylolisthesis	1	0	0	0
Ear disorders	0	1	1	1
Vertigo	0	1	0	1
Merniere's disease	0	0	1	0
Hepatobiliary disorders	3	2	0	1
Cholecystitis	0	0	0	1
Chronic cholecystitis	0	1	0	0
Choelithiasis	1	1	0	0
Bile duct stone	1	0	0	0
Portal vein thrombosis	1	0	0	0
Renal disorders	1	0	2	1
Acute renal failure	0	0	2	1
Calculus ureteric	1	0	0	0
Investigations	0	1	0	1
Increased blood glucose	0	1	0	0
Increased blood pressure	0	0	0	1
Psychiatric disorders	2	0	0	2
Confusional state	0	0	0	1

	RQ4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Psychotic disorder	0	0	0	1
Mental status changes	2	0	0	0
Blood disorders	0	0	0	1
Anemia	0	0	0	1
Congenital disorders	0	0	0	1
AV malformation	0	0	0	1
Reproductive disorders	0	1	0	0
Cystocele	0	1	0	0

VIEW #2: Ocular Treatment Emergent SAEs in the Study Eye (Safety Analysis Set)

	RQ4	2Q4	0.5Q4	2Q8
Visual Acuity Reduced	1	1	1	5
Retinal hemorrhage	1	2	1	1
Cataract	1	1	0	1
IOP increased	0	0	1	1
RPE tear	1	0	1	1
Cataract nuclear	0	1	0	0
Macular cyst	0	0	0	1
Macular degeneration	0	0	0	1
Macular hole	0	0	1	0
Macular scar	0	1	0	0
Retinal detachment	1	0	1	0
Retinal pigment epitheliopathy	0	0	1	0
Cataract cortical	1	0	0	0
Hyphema	1	0	0	0
PCO	2	0	0	0
Retinal degeneration	1	0	0	0

VIEW #2: Non-Ocular Treatment Emergent SAEs (Safety Analysis Set)

	RQ4	2Q4	0.5Q4	2Q8
Number of Subjects With At Least 1 Non-ocular SAE	26 (8.9%)	36 (11.7%)	37 (12.5%)	38 (12.2%)
Blood disorders				
Anemia	0	1	1	0
Febrile neutropenia	0	0	0	1
Cardiac disorders				
Acute coronary syndrome	5	8	7	11
Acute myocardial infarction	0	2	2	1
Angina pectoris	1	0	0	1
Arteriosclerosis coronary artery	0	0	0	1
A fib	2	1	0	3
A flutter	0	0	0	1
AV block	0	0	1	0
Cardiac arrest	0	0	0	1
Cardiac failure	0	0	0	1
Cardiovascular insufficiency	0	0	0	1
CAD	0	0	0	1
Myocardial infarction	2	0	3	3
Myocardial ischemia	0	0	0	1
Palpitations	0	1	0	0

	RQ4	2Q4	0.5Q4	2Q8
Pericarditis	0	1	0	0
Supraventricular tachycardia	0	1	0	0
Ear disorders				
Tympanic membrane disorders	1	0	1	0
Vertigo	0	0	1	0
GI disorders				
Anal fistula	0	0	1	0
Colitis	0	1	0	0
Constipation	0	0	0	1
Diverticulum intestinal	0	0	0	1
Gastric ulcer	0	0	1	0
Gastritis	0	1	0	0
Gastritis erosive	0	0	1	1
Inguinal hernia	0	1	1	1
Intestinal obstruction	0	0	1	0
Large intestine perforation	0	0	0	1
Lower gastrointestinal hemorrhage	0	1	0	0
Pancreatitis acute	0	0	1	1
Small intestinal obstruction	0	0	1	0
General disorders				
Chest pain	1	1	0	0
Death	0	0	1	0
Device dislocation	1	1	0	0
Device malfunction	0	1	0	0
Edema peripheral	1	0	0	1
Pyrexia	0	1	0	0
Heptobiliary disorders				
Cholecystitis	0	1	0	0
Cholecystitis acute	0	1	0	0
Cholelithiasis	0	0	1	0
Infections				
Appendicitis	1	0	0	0
Bronchitis	1	1	0	1
Dysentery	1	0	0	0
Escherichia sepsis	0	0	0	1
Gastroenteritis	0	0	0	1
Gastroenteritis norovirus	1	0	0	0
Gastroenteritis salmonella	0	0	0	1
Pneumonia	0	2	0	2
Pneumonia pneumococcal	0	1	0	0
Post-operative wound infection	0	0	0	1
Respiratory tract infection	1	0	0	0
Septic shock	0	0	0	1
UTI	1	1	0	0
Injury				
Accident	0	0	1	0
Ankle fracture	0	0	0	1
Burns second degree	0	0	1	0
Clavicle fracture	0	0	0	1
Concussion	0	0	0	1

	RQ4	2Q4	0.5Q4	2Q8
Contusion	0	0	1	0
Fall	2	0	1	0
Femoral neck fracture	0	0	1	0
Femur fracture	0	0	0	1
Graft thrombosis	0	0	0	1
Head injury	0	1	0	0
Joint injury	1	0	0	0
Lower limb fracture	0	0	1	0
Lumbar vertebral fracture	0	0	0	1
Meniscus lesion	0	0	0	1
Post procedural complication	0	0	1	0
Radius fracture	0	1	0	0
Road traffic accident	0	1	0	1
Skull fractured base	0	1	0	0
Subdural hematoma	0	1	0	0
Upper limb fracture	0	0	2	0
Wound hemorrhage	0	0	0	1
Investigations				
Blood osmolarity decreased	0	1	0	0
EKC QT prolonged	0	1	0	0
Metabolism disorders				
Dehydration	1	0	0	0
Diabetes mellitus	1	0	0	0
Hyperglycemia	1	0	0	0
Musculoskeletal disorders				
Arthralgia	0	1	0	0
Arthritis	0	0	0	1
Dupuytren's contracture	1	0	0	0
Intervertebral disc protrusion	1	0	0	0
Neck pain	0	1	0	0
Rheumatoid arthritis	0	1	0	0
Sjogren's syndrome	0	0	0	1
Synovitis	0	0	0	1
Neoplasms				
AML	0	0	0	1
Basal cell CA	1	0	2	0
Bladder CA	0	0	1	0
Bladder CA recurrent	0	0	1	0
Breast CA	1	0	3	1
Colon CA	0	1	0	0
Colon CA recurrent	0	1	0	0
Lung CA metastatic	0	0	0	1
Lung CA stage 4	0	0	0	1
Lung neoplasm malignant	0	0	1	0
Esophageal CA	1	0	0	0
Ovarian CA	0	1	0	0
Prostate CA	0	0	1	0
Squamous cell CA	0	0	0	1
Nervous system disorders				
Brain edema	0	1	0	0
Cerebral infarction	0	0	1	0

	RQ4	2Q4	0.5Q4	2Q8
CVA	1	1	0	2
Epilepsy	0	1	0	0
HA	0	1	0	0
Hypertensive encephalopathy	0	0	0	1
Lacunar infarct	0	1	0	0
Nerve root compression	1	0	0	0
Petit mal seizure	0	0	1	0
Syncope	0	1	0	0
TIA	0	2	0	0
7th nerve palsy	0	1	0	0
Renal disorders				
Renal failure	0	1	0	1
Urinary tract obstruction	0	0	0	1
Reproductive disorders				
BPH	0	0	0	1
Uterine hemorrhage	0	1	0	0
Respiratory disorders				
Acute pulmonary edema	1	0	0	0
COPD	0	1	0	1
Cough	0	1	0	0
Dyspnea	0	0	0	1
Pleurisy	0	0	1	0
Pneumothorax	0	1	0	0
Sleep apnea	0	1	0	0
Skin disorders				
Dermal cyst	0	0	1	0
Dermatitis allergic	0	0	0	1
Erythema mutifome	0	0	1	0
Rash	0	1	0	0
Skin necrosis	1	0	0	0
Skin ulcer	1	0	0	0

Study VGFT-OD-0702: Ocular SAEs in the Study Eye (All Enrolled Set)

	N=157
VA reduced	4
Retinal hemorrhage	2
Cataract	1
Retinal edema	1
Corneal abrasion	1

Study VGFT-OD-0702: Non-Ocular SAEs (All Enrolled Set)

	N=157
Neoplasms	
Squamous cell of skin	4
Colon CA	2
Head and neck CA	2
Lung CA	2
Prostate CA	2

Bladder CA	1
Breast CA	1
Breast CA recurrent	1
CLL	1
Liver CA	1
Non-small cell lung CA	1
Renal cell CA	1
Small cell lung CA	1
Squamous cell CA	1
Transitional cell CA	1
Cardiac disorders	
A fib	5
Coronary artery stenosis	2
Myocardial infarction	2
Angina pectoris	1
Arteriosclerosis	1
AV block	1
Bradycardia	1
CHF	1
CAD	1
Pericarditis	1
Infections	
Pneumonia	3
Bronchitis	2
Cellulitis	1
C. diff colitis	1
Gastroenteritis	1
Sepsis	1
UTI	1
Viral infection	1
Nervous system disorders	
CVA	2
Dementia	2
Basal ganglia hemorrhage	1
Carotid artery stenosis	1
Dizziness	1
HA	1
Lacunar infarction	1
Pre-syncope	1
Syncope	1
TIA	1
GI disorders	
Colonic polyp	1
Diarrhea	1
Duodenal ulcer perforation	1
Enteritis	1
Gastric ulcer	1
Inguinal hernia	1
Intestinal obstruction	1
Injury	
Fall	5
Cervical vertebral fracture	1

Concussion	1
Femoral neck fracture	1
Incisional hernia	1
Periorbital hematoma	1
Pubis fracture	1
Respiratory disorders	
Pulmonary embolism	2
COPD	1
Dsypnea	1
Pleural effusion	1
Pulmonary edema	1
Respiratory failure	1
Musculoskeletal disorders	
Osteoarthritis	2
Arthralgia	1
Intervertebal disc protrusion	1
Lumbar spinal stenosis	1
Rotator cuff syndrome	1
Hepatobiliary disorders	
Cholelithiasis	3
Bile duct stone	1
Cholecystitis acute	1
General disorders	
Death	1
Gait disorders	1
Metaplasia	1
Metabolism disorders	
Dehydration	3
Psychiatric disorders	
Hallucination	1
Mental disorder	1
Renal disorders	
Hematuria	1
Renal failure	1
Vascular disorders	
HTN	1
Orthostatic hypotension	1
Blood disorders	
Anemia	1
Endocrine disorders	
Goiter	1
Immune system disorders	
Sarcoidosis	1
Reproductive system disorders	
Prostatic obstruction	1

Dropouts

VIEW #1: Disposition (All Randomized Subjects)

	RQ4	**2Q4**	**0.5Q4**	**2Q8**
Randomized	306	304	304	303
Completed first year of study	284 (92.8%)	293 (96.4%)	277 (91.1%)	276 (91.1%)
Discontinuation form study with first year	22	11	27	27
Adverse event	4	3	5	4
Death	3	1	2	7
Withdrawal by subject	10	5	7	8
Protocol deviation	3	0	3	1
Lost to follow-up	1	2	4	4
Treatment failure	0	0	2	2
Other	1	0	4	1

VIEW #2: Disposition (All Randomized Subjects)

	RQ4	**2Q4**	**0.5Q4**	**2Q8**
Randomized	303	313	311	313
Completed first year of study	276 (91.1%)	281 (89.8%)	274 (88.1%)	284 (90.7%)
Discontinuation from study with first year	27	32	37	29
Adverse event	2	6	8	9
Death	1	3	2	1
Withdrawal by subject	11	15	13	11
Protocol deviation	2	1	1	0
Lost to follow-up	4	1	2	2
Treatment failure	0	0	1	1
Other	7	6	10	5

Study VGFT-OD-0702: Disposition (All Enrolled Set)

	N=149
Subjects Prematurely Terminated From Study	28
Withdrawn Due to AE	4
Investigator Decision	2
Subject Request for Withdrawal	8
Lost to f/u	3
Death	7
Other	4

Overall Listing of Serious Adverse Events

A treatment-emergent adverse event was defined as an event that was observed or reported after administration of study drug that was not present prior to study drug administration or an event that represented an exacerbation of a pre-existing event.

VIEW #1: Ocular Treatment Emergent AE in the Study Eye Occurring In At Least >=5% of Subjects (Safety Analysis Set)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=304**	**2Q8 N=303**
Number of subjects with at least 1 ocular TEAE in study eye	246	228	226	238
Conjunctival hemorrhage	144	109	120	131
Vitreous floaters	33	40	23	21
Eye pain	26	33	27	22
Vitreous detachment	24	26	23	19
Visual acuity reduced	20	24	23	20
Retinal hemorrhage	19	9	17	23
Retinal pigment epitheliopathy	11	16	15	13
Macular degeneration	16	16	17	10
IOP increased	22	14	12	15
Eye irritation	16	13	13	12
Maculopathy	19	10	20	8
FBS	9	8	9	16

VIEW #1: Non-Ocular Treatment Emergent AE in the Study Eye Occurring In At Least >=2% of Subjects (Safety Analysis Set)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=304**	**2Q8 N=303**
Number of subjects with at least 1 non-ocular TEAE in study eye	234	220	231	223
Infections	123	96	102	104
Nasopharyngitis	23	33	24	26
Upper respiratory tract infection	13	11	14	18
UTI	17	14	15	13
Bronchitis	16	12	11	17
Sinusitis	8	7	11	11
Influenza	9	7	3	7
Pneumonia	14	5	4	6
Cellulitis	7	3	6	2
Investigations	48	57	59	60
Blood glucose increased	8	9	11	7
Protein urine present	7	7	7	10
Urine protein/creatinine ratio increased	3	6	9	6
Blood urine present	4	7	5	6
Blood pressure increased	4	5	3	9
Nervous system disorders	35	40	47	47
HA	19	11	11	12
Dizziness	5	8	6	7

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Injury	42	33	47	45
Fall	15	14	12	16
Contusion	4	1	7	3
GI disorder	52	39	37	40
Nausea	13	12	10	7
Diarrhea	9	11	7	5
GERD	6	2	8	6
Constipation	12	3	5	6
Musculoskeletal disorders	54	30	38	41
Arthralgia	11	10	12	5
Back pain	9	5	6	9
Osteoarthritis	5	1	4	7
Arthritis	9	3	5	2
Respiratory disorders	47	34	25	36
Cough	11	7	2	10
COPD	6	5	5	7
Dyspnea	8	4	5	3
Cardiac disorders	41	30	29	32
A fib	11	5	4	6
Vascular disorders	34	30	26	28
HTN	25	21	21	20
Metabolism disorders	29	24	26	24
Hypercholesterolemia	5	3	5	7
Skin disorders	22	16	25	20
General disorder and administration site condition	19	20	16	22
Neoplasms	22	15	21	22
Basal cell CA	4	4	8	8
Renal disorders	19	11	19	15
Psychiatric disorders	21	10	15	14
Anxiety	7	2	3	4
Immune disorders	8	10	12	16
Seasonal allergy	4	6	9	9
Blood disorders	10	6	14	9
Ear disorders	7	7	6	11
Vertigo	4	5	3	8
Reproductive disorders	3	4	8	7

VIEW #2: Ocular Treatment Emergent AE in the Study eye Occurring in at least >=5% of Subjects (Safety Analysis Set)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=297**	**2Q8 N=307**
Number of subjects with at least 1 ocular TEAE in study eye	187	191	182	198
Visual acuity reduced	20	26	34	33
Conjunctival hemorrhage	23	24	37	30
Retinal hemorrhage	29	27	30	27
Macular degeneration	23	27	23	30
Eye pain	27	33	22	21
IOP increased	19	24	15	15
Detachment of RPE	15	18	15	12
Vitreous detachment	9	18	9	15
Cataract	15	16	12	12
Ocular hyperemia	18	12	13	9
Retinal degeneration	11	17	9	7

VIEW #2: Non-Ocular Treatment Emergent AE in the Study eye Occurring in at least >=2% of Subjects (Safety Analysis Set)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=304**	**2Q8 N=303**
Number of subjects with at least 1 non-ocular TEAE in study eye	181	231	206	213
Infections	77	72	67	73
Nasopharyngitis	25	14	25	19
Influenza	7	14	8	17
Bronchitis	7	13	9	9
UTI	9	7	6	5
Cystitis	3	6	6	2
Upper respiratory tract infection	6	3	5	5
Investigations	43	63	55	61
Blood glucose increased	1	12	8	8
EKG T wave inversion	5	9	2	7
Cardiac disorders	32	48	35	40
AV first degree block	10	20	14	9
A fib	3	7	1	5
GI disorders	30	40	34	45
Diarrhea	10	8	10	14
Abdominal pain	0	3	1	1
Vomiting	6	4	3	2
Musculoskeletal disorders	31	36	33	39
Back pain	13	14	9	11
Arthralgia	8	7	10	3
Osteoarthritis	4	5	5	6
Nervous system disorders	27	33	26	35
HA	11	9	12	17
Dizziness	9	5	1	3

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Vascular disorders	247	33	24	23
HTN	22	22	18	16
Respiratory disorders	24	25	25	24
Cough	7	2	7	3
Injury	19	18	26	27
Fall	9	3	4	2
General disorders	**18**	22	29	13
Pyrexia	8	8	15	5
Metabolism disorders	12	19	16	23
DM	4	7	2	7
Hyperglycemia	2	2	6	2
Skin disorders	18	20	14	14
Renal disorders	5	9	11	13
Psychiatric disorders	7	7	11	10
Blood disorders	11	5	12	10
Anemia	6	4	8	7
Neoplasms	6	8	10	8
Ear disorders	4	7	8	9
Reproductive disorders	4	5	4	8
Surgical procedures	4	7	2	3

Study VGFT-OD-0702: Ocular Treatment Emergent Reported by >3 Subjects in the Study Eye (All Randomized Set)

	Vial N=50	PFS N=99
Number of subjects with events	38	58
Retinal hemorrhage	8	8
Cataract	7	9
VA reduced	8	7
Conjunctival hemorrhage	6	8
Vitreous floaters	2	7
Blepharitis	5	2
Macular degeneration	3	4
FBS	0	6
Vitreous detachment	5	1
Eye pain	1	3
Eye pruritis	0	4
Injection site pain	0	4
IOP increased	0	4

Study VGFT-OD-0702: Non-Ocular Treatment Emergent AE Reported by >3 Subjects in the Study eye Occurring (All Randomized Set)

	Vial N=50	**PFS N=99**
Number of subjects with events	44	87
Blood disorders	1	6
Anemia	1	4
Cardiac disorders	4	12
A fib	2	2
Ear disorders	4	3
Vertigo	2	3
GI disorders	14	28
Diarrhea	5	5
Nausea	3	4
Vomiting	4	1
GERD	2	2
Dyspepsia	1	3
Hepatobiliary disorders	0	5
Cholelithiasis	0	4
Immune system disorder	1	9
Seasonal allergy	0	7
Infections	24	46
Nasopharyngitis	5	11
Bronchitis	5	9
UTI	6	7
Sinusitis	2	8
Upper respiratory tract infection	4	5
Influenza	2	4
Pneumonia	2	4
Localized infection	0	4
Injury	12	23
Fall	9	10
Contusion	3	2
Rib fracture	1	3
Investigations	10	32
Protein urine present	4	2
WBC increased	2	4
Blood pressure increased	0	4
WBC urine positive	0	4
Metabolism disorders	8	14
Hypercholesterolemia	2	2
DM	2	1
Gout	1	2
Dehydration	1	1
DM inadequate control	0	1
Musculoskeletal disorders	13	29

	Vial N=50	**PFS N=99**
Arthritis	2	6
Osteoarthritis	4	4
Arthralgia	2	5
Back pain	2	3
Pain in extremity	2	3
Osteoporosis	0	4
Bursitis	2	2
Neoplasm	5	19
Basal cell CA	1	5
Squamous cell CA of skin	2	2
Nervous system disorders	11	21
Dementia	2	3
Dizziness	1	4
Psychiatric disorders	5	11
Depression	1	4
Insomnia	2	3
Respiratory disorders	8	14
Cough	3	4
Dyspnea	1	3
Skin disorders	2	14
Rash	0	4
Vascular disorders	4	14
HTN	1	11

Special Safety Studies

Nasomucosal examination (ENT sub-study)

A subset of 160 subjects in VIEW #2 were additionally examined by an ENT specialist, including nasal endoscopy (ENT sub-study). The aim of this sub-study was to investigate potential nasomucosal side effects and the potential relationship to the study drug. It was performed in a subset of subjects (90 subjects per group, total group n = 360) from selected centers with the goal to include a minimum of 240 evaluable subjects across all arms. The sub-study referred only to subjects who had signed a separate informed consent in this regard. The purpose of the ENT sub-study was to better define potential nasomucosal side effects which were reported as histopathologic findings in a toxicology study (VGFT-TX-0511 or COV7369-112). Mucosal symptoms were also observed during ocular or systemic therapy with other anti-VEGF products, (ie. in the Lucentis prescribing information nasopharyngitis is mentioned as a frequently reported non-ocular adverse event). Nasal symptoms are very common in the general population - allergic rhinitis alone has a lifetime prevalence of 20 to 25%. Therefore, a targeted, standardized medical history was taken concerning chronic airway diseases, prior to study treatment at Visit 2 by an ENT specialist. A careful endoscopy of the nasal airways with a standardized documentation of findings was to complete the rhinological investigation of Visit 2. At Visit 6 and Visit 16, the participants were reevaluated by an ENT specialist. The ENT specialist had to ask for nose bleeds and new nasal symptoms since the last ENT visit, and a nasal endoscopy was performed.

VIEW #2: ENT Sub-Study (Subjects with ENT Treatment Emergent AEs)

	R0.5Q4	2Q4	0.5Q4	2Q8
Nasal septum deviation	4	2	0	5
Nasal mucosal disorder	1	1	2	4
Rhinorrhea	0	1	2	4
Epistaxis	1	1	1	3
Nasal polyps	1	1	1	2
Nasal turbinate hypertrophy	0	0	1	2
Nasal dryness	0	0	0	1
Nasal mucosal discoloration	0	0	1	1
Nasal edema	0	0	0	1
Paranasal cyst	0	0	1	1
Rhinitis hypertrophy	1	0	0	0
Nasopharyngitis	5	2	4	8
Upper respiratory tract infection	1	1	1	4
Rhinitis	2	0	1	1
Viral rhinitis	0	0	1	1
Acute tonsillitis	1	0	0	0

Arterial Thromboembolic Events

VIEW#1: Number of Subjects with APTC Arterial Thromboembolic Events through Year 1 (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Any APTC event	5 (1.7%)	2 (0.7%)	7 (2.3%)	6 (2.0%)
Non-fatal myocardial infarctions	4	1	4	1
Non-fatal strokes	0	1	2	1
Vascular deaths	1	0	1	4

VIEW#2: Number of Subjects with APTC Arterial Thromboembolic Events through Year 1 (Safety Analysis Set)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Any APTC event	5 (1.7%)	4 (1.3%)	5 (1.7%)	8 (2.6%)
Non-fatal myocardial infarctions	2	2	2	5
Non-fatal strokes	2	1	1	2
Vascular deaths	1	1	2	1

IOP Analysis

Number of Subjects with An Absolute Value of IOP >=35mmHg During the Study (Safety Analysis Set)

View #1	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Any Visit	13	13	7	13

View #2	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Any Visit	9	9	4	5

Proportion of Subjects with >=10mmHg Increase in IOP From Baseline to Any Pre-Dose Measurement (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Pre-dose from baseline	12	5	6	7

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Pre-dose from baseline	7	3	8	7

VIEW #1: Proportion of Subjects with Greater Than or Equal to 10mmHg Increase in IOP (Safety Analysis Set)

		R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Baseline	Post-dose from pre-dose	24	28	14	25
Week 1	Pre-dose from baseline	1	1	0	0
Week 4	Pre-dose from baseline	0	0	0	2
	Post-dose from pre-dose	23	28	24	24
Week 8	Pre-dose from baseline	2	1	1	0
	Post-dose from pre-dose	25	26	20	27
Week 12	Pre-dose from baseline	0	0	1	0
	Post-dose from pre-dose	19	27	25	0
Week 16	Pre-dose from baseline	0	0	1	2
	Post-dose from pre-dose	27	27	25	16
Week 20	Pre-dose from baseline	1	0	0	1
	Post-dose from pre-dose	24	28	17	5
Week 24	Pre-dose from baseline	1	0	2	1
	Post-dose from pre-dose	15	36	17	25
Week 28	Pre-dose from baseline	2	0	1	0
	Post-dose from pre-dose	20	22	18	9
Week 32	Pre-dose from baseline	0	2	3	1
	Post-dose from pre-dose	23	29	15	32
Week 36	Pre-dose from baseline	1	1	0	2
	Post-dose from pre-dose	31	28	22	1
Week 40	Pre-dose from baseline	2	1	1	2
	Post-dose from pre-dose	25	32	18	21
Week 44	Pre-dose from baseline	1	0	0	0
	Post-dose from pre-dose	17	29	18	5
Week 48	Pre-dose from baseline	0	0	1	2
	Post-dose from pre-dose	23	17	19	31
Week 52	Pre-dose from baseline	4	0	1	1
	Post-dose from pre-dose	4	2	4	4

VIEW #2: Proportion of Subjects with Greater Than or Equal to 10mmHG Increase in IOP (Safety Analysis Set)

		R0.5Q4 N291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Baseline	Post-dose from pre-dose	8	10	2	8
Week 1	Pre-dose from baseline	0	0	1	3
Week 4	Pre-dose from baseline	1	0	0	0
	Post-dose from pre-dose	5	11	3	8
Week 8	Pre-dose from baseline	1	0	1	0
	Post-dose from pre-dose	8	8	5	12
Week 12	Pre-dose from baseline	1	0	1	1
	Post-dose from pre-dose	7	8	7	1
Week 16	Pre-dose from baseline	0	0	2	2
	Post-dose from pre-dose	12	6	7	7
Week 20	Pre-dose from baseline	1	0	0	2
	Post-dose from pre-dose	13	8	2	1
Week 24	Pre-dose from baseline	0	0	1	0
	Post-dose from pre-dose	8	5	5	6
Week 28	Post-dose from pre- dose	8	10	4	1
Week 32	Post-dose from pre-dose	6	7	6	5
Week 36	Pre-dose from baseline	2	0	0	3
	Post-dose from pre-dose	10	9	4	2
Week 40	Pre-dose from baseline	2	1	1	1
	Post-dose from pre-dose	7	7	3	7
Week 44	Pre-dose from baseline	1	0	0	0
	Post-dose from pre-dose	8	6	6	1
Week 48	Pre-dose from baseline	2	1	3	1
	Post-dose from pre-dose	8	7	5	3
Week 52	Pre-dose from baseline	0	0	1	1
	Post-dose from pre-dose	3	0	1	2

Immunogenicity

For both VIEW #1 and VIEW #2 samples for ADA (anti-drug-antibody) were taken at Screening and subsequently on Weeks 12, 24, 36, and 52. All samples were drawn prior to injection of study drug.

VIEW#1: Number of Subjects with Anti-VEGF Trap Antibodies By Treatment Group (Safety Analysis Set)

	RQ4 N=304	**2Q4 N=304**	**0.5Q4 N=304**	**2Q8 N=303**
Negative	287	291	290	297
Positive	15 (4.9%)	13 (4.3%)	11 (3.6%)	6 (2.0%)
Not drug induced	5	3	8	6
Transient	7	7	3	5
Persistent	3	3	0	1
Missing*	2	0	3	0

*Subjects with no sample collection of subjects with missing post-baseline sample.

VIEW#2: Number of Subjects with Anti-VEGF Trap Antibodies By Treatment Group (Safety Analysis Set)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=297**	**2Q8 N=307**
Negative	280	285	277	303
Positive	8 (2.7%)	15 (4.9%)	16 (5.4%)	3 (1.0%)
Not drug induced	3	8	8	1
Transient	3	2	4	1
Persistent	2	5	4	1
Not applicable	3	9	4	1

Post-marketing Experience

Because aflibercept is not marketed in any country, no sources of AE information exist, except for clinical study reports of the trials that were conducted for its development.

Draft Questions for the Advisory Committee

1) Do you think adequate safety and efficacy for aflibercept injection has been demonstrated for the treatment of neovascular AMD?

2) If yes, on which study(ies) are you basing your decision?

3) If not, what additional study(ies) should be performed? Do you have any suggestions regarding trial design?

4) What dosing should be approved (0.5mg Q4, 2mg Q4, or 2mg Q8)? If recommend approving a Q8 schedule should patients be monitored Q4?

5) Elevations in IOP following repeated dosing of VEGF-inhibitors has been reported in the literature and is seen in low frequency in the trials of aflibercept, do you have recommendations of ways to handle the issue?

6) Do you have any suggestions concerning the proposed draft labeling of the product?

Draft Labeling for Discussion

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EYLEA safely and effectively. See full prescribing information for EYLEA.
EYLEA™ (aflibercept injection)
Intravitreal Injection
Initial U.S. Approval: 201X

INDICATIONS AND USAGE

EYLEA™ (aflibercept injection) is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD). (1)

DOSAGE AND ADMINISTRATION

For ophthalmic intravitreal injection only (2.1)
The recommended dose for EYLEA is 2 mg (50 microliters) administered by intravitreal injection once every 2 months, following 3 initial monthly injections of 2 mg (50 microliters). EYLEA may be dosed as frequently as 2 mg once per month. (2.2)

DOSAGE FORMS AND STRENGTHS

40 mg/mL solution for intravitreal injection in a single-use, sterile, pre-filled, glass syringe (3)
40 mg/mL solution for intravitreal injection in a single-use, glass vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4)
- Active severe intraocular inflammation (4)
- Hypersensitivity (4)

WARNINGS AND PRECAUTIONS

- Endophthalmitis may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)

ADVERSE REACTIONS

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-877-REGN-777 (1-877-734-6777) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 0 for PATIENT COUNSELING INFORMATION

Revised: xx/201x

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

EYLEA™ (aflibercept injection) is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD).

2. DOSAGE AND ADMINISTRATION

2.1. General Dosing Information

EYLEA IS FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY. It must only be administered by a qualified physician experienced in administering intravitreal injections.

2.2. Dosing

The recommended dose for EYLEA is 2 mg (50 microliters) administered by intravitreal injection once every 2 months, following 3 initial monthly injections of 2 mg (50 microliters). EYLEA may be dosed as frequently as 2 mg once per month. [*See Clinical Studies (14).*]

2.3. Preparation for Administration

ELYEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial or pre-filled syringe must not be used.

The unopened vial or blister pack of EYLEA should be stored refrigerated temperatures. After opening the vial or blister pack, proceed under aseptic conditions.

For the intravitreal injection, the 30-gauge x ½-inch injection needle should be used and sterile field should be created.

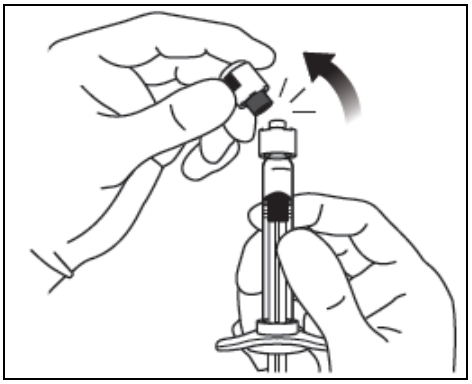
Pre-Filled Syringe

The pre-filled syringe is for single use only.

Administration of EYLEA involves assembly of the pre-filled glass syringe included in the sterilized blister pack with the injection needle included in the carton.

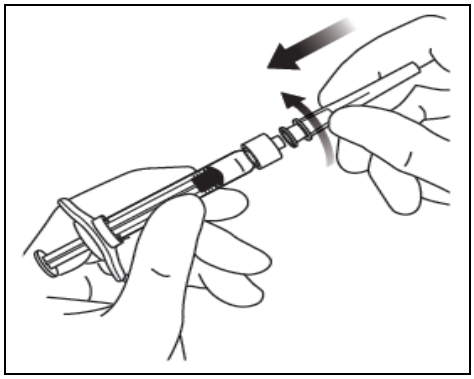
1. When ready to administer EYLEA, open the carton and remove the injection needle and sterilized blister pack. Carefully peel open the sterilized blister pack. Keep the syringe in the sterile tray until you are ready for assembly.
2. To remove the syringe cap, hold the syringe in one hand while using your other hand to grasp the syringe cap with the thumb and forefinger. **Snap off (do not turn or twist)** the syringe cap (see Figure 1). Place the syringe back in the sterile tray or on a sterile field.

Figure 1:



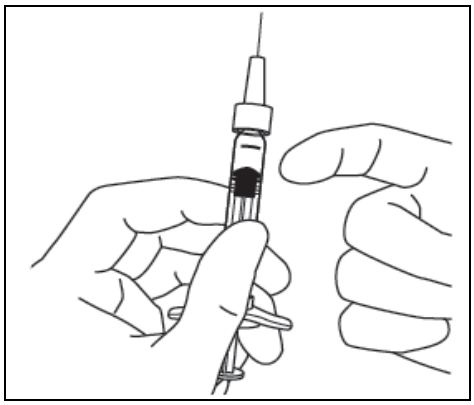
3. To avoid compromising the sterility of the product, do not pull back on the plunger.
4. Remove the 30-gauge x ½-inch injection needle from the plastic pouch and attach to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 2).

Figure 2:



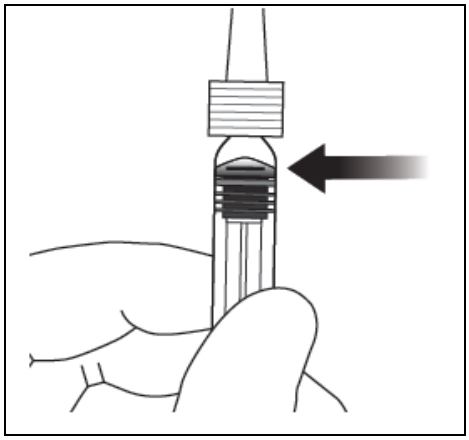
5. When ready to administer EYLEA, remove the plastic needle shield from the needle.
6. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 3).

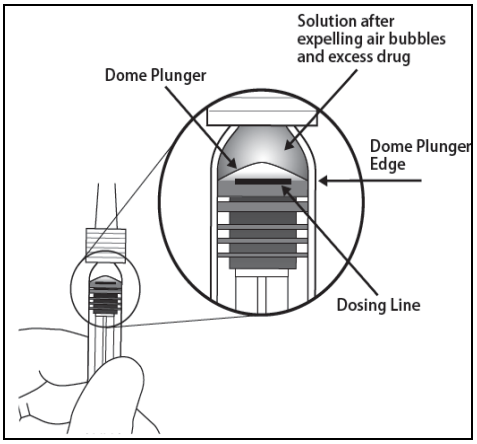
Figure 3:



7. To eliminate all bubbles and to expel excess drug, SLOWLY depress the plunger to align the cylindrical base of the domed tip with the black dosing line (equivalent to 50 microliters) on the syringe (see Figure 4 and 5).

Figure 4: **Figure 5:**



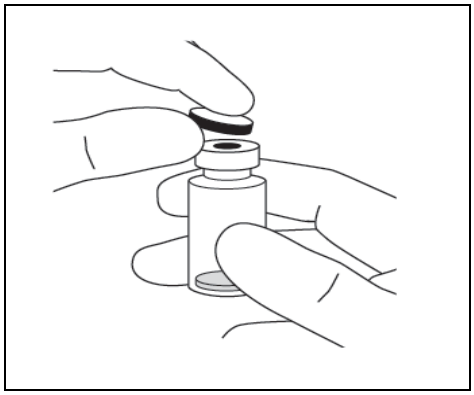


Vial

The glass vial is for single use only.

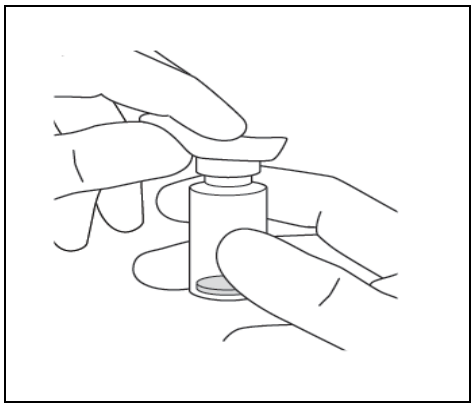
1. Remove the protective plastic cap from the vial (see Figure 6).

Figure 6:



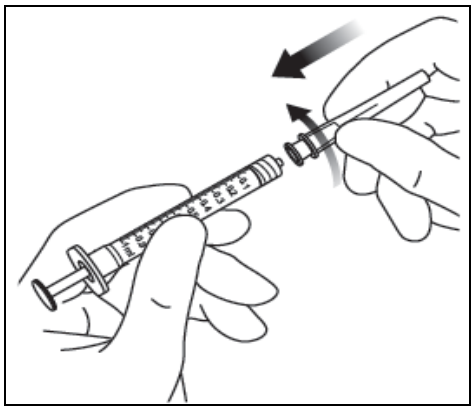
2. Clean the top of each vial with an alcohol wipe (see Figure 7).

Figure 7:



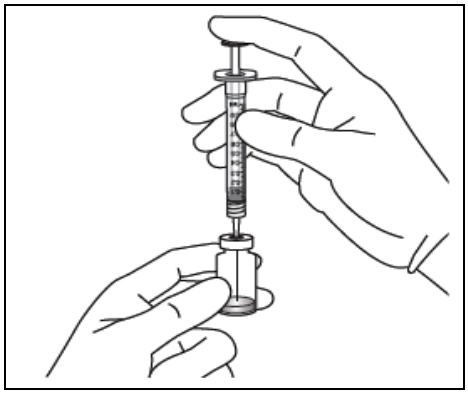
3. Remove the 19-gauge x 1½-inch, 5-micron, filter needle from its pouch and remove the 1-mL syringe supplied in the carton from its pouch. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip (see Figure 8).

Figure 8:



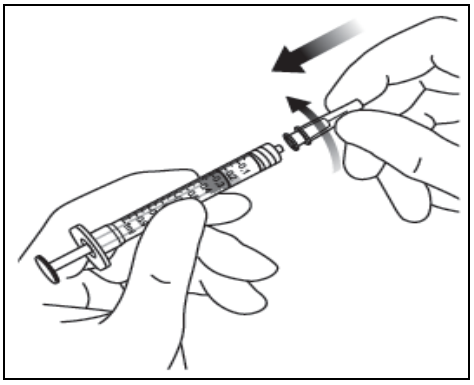
4. Push the filter needle into the center of the vial stopper until the needle touches the bottom edge of the vial.
5. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal (see Figure 9).

Figure 9:



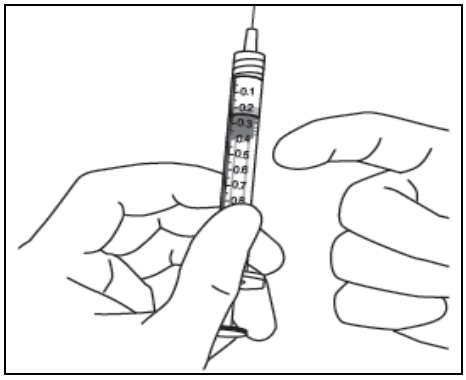
6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
7. Remove the filter needle from the syringe and properly dispose of the filter needle.
   Note: Filter needle is **not** to be used for intravitreal injection.
8. Remove the 30-gauge x ½-inch injection needle from the plastic pouch and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 10).

Figure 10:



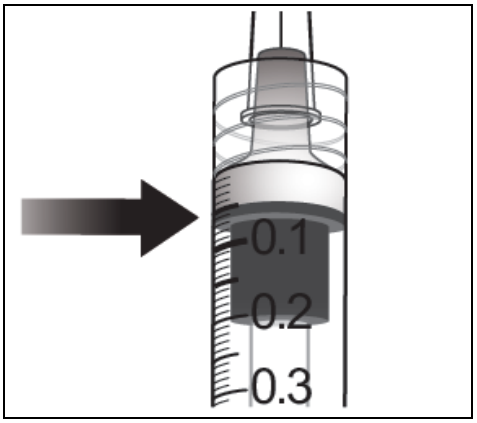
9. When ready to administer EYLEA, remove the plastic needle shield from the needle.
10. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 11).

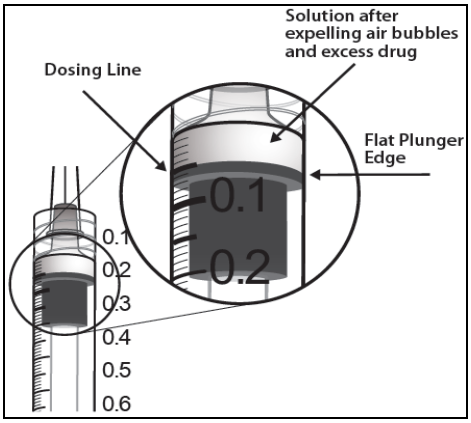
Figure 11:



11. To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.05 mL (50 microliters) on the syringe (see Figure 12 and 13).

Figure 12:
Figure 13:





2.4. Administration

Intravitreal injections must be carried out according to medical standards and applicable guidelines (for example, by a qualified physician experienced in administering intravitreal injections). The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide (e.g., povidone iodine) should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay [*see Patient Counseling Information (0)*].

Each pre-filled syringe or vial should only be used for the treatment of a single eye.

After injection, any unused product must be discarded.

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

3. DOSAGE FORMS AND STRENGTHS

Single-use, sterile, pre-filled, glass syringe designed to deliver 0.05 mL (50 microliters) of 40 mg/mL solution for intravitreal injection.

Single-use, glass vial designed to provide 0.05 mL (50 microliters) of 40 mg/mL solution for intravitreal injection.

4. CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periocular infection
- Active severe intraocular inflammation
- Known hypersensitivity to aflibercept or to any of the excipients in EYLEA

5. WARNINGS AND PRECAUTIONS

5.1. Endophthalmitis

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay and should be managed appropriately [*see Dosage and Administration (2.4) and Patient Counseling Information (0)*].

5.2. Increase in Intraocular Pressure

Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Special precaution is needed in patients with poorly controlled glaucoma. In all cases both intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately [*see Dosage and Administration (2.4)*].

5.3. Thromboembolic Events

Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.

ATEs, as defined by APTC criteria, include nonfatal myocardial infarction, nonfatal stroke, or vascular death (including deaths of unknown cause). The incidence in the VIEW1 and VIEW2 wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.7% (10 out of 595) in patients treated with ranibizumab [*see Clinical Studies (14)*].

6. ADVERSE REACTIONS

The following adverse reactions are discussed in detail in other sections of the labeling:

- Endophthalmitis [*see Warnings and Precautions (5.1)*]
- Increased intraocular pressure [*see Warnings and Precautions (5.2)*]

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

6.1. Injection Procedure

Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with either EYLEA or ranibizumab and included endophthalmitis, traumatic cataract, and transient increased intraocular pressure.

6.2. Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months [*see Clinical Studies (14)*].

Table 1: Most Common Adverse Reactions (≥1%) in Phase 3 wet AMD studies

Adverse Reactions	EYLEA (n=1824)	Ranibizumab (n=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Conjunctival hyperemia	4%	8%
Corneal erosion	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	2%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were retinal detachment, retinal tear, hypersensitivity, and endophthalmitis.

7. DRUG INTERACTIONS

No formal drug interaction studies have been performed with EYLEA.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Pregnancy Category C

Observed Adverse Effect Level (NOAEL) was at the dose of 3 mg/kg. At this dose, the systemic exposures based on C_{max} and AUC for free aflibercept were approximately 2900- and 600-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. Studies in animals have shown reproductive toxicity after systemic administration. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Aflibercept produced embryo-fetal toxicity in an embryo-fetal development study in pregnant rabbits with intravenous administration (3 to 60 mg/kg). The maternal No

8.3. Nursing Mothers

It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4. Pediatric Use

The safety and efficacy of EYLEA have not been studied in these age groups.

8.5. Geriatric Use

In the clinical studies, approximately 89% (1616/1817) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 63% (1139/1817) were ≥75 years of age.

11. DESCRIPTION

EYLEA™ (aflibercept injection) is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

EYLEA is a sterile, clear, and colorless to pale yellow, iso-osmotic solution. EYLEA is supplied as a preservative-free, sterile, aqueous solution in a single-use, sterile, pre-filled, glass syringe or single-use, glass vial designed to deliver 0.05 mL (50 microliters) of EYLEA (40 mg/mL) with 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularization and excessive vascular permeability.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors. The equilibrium dissociation constant (K_D) for aflibercept binding to human VEGF-A_{165} is 0.5 pM and to human VEGF-A_{121} is 0.36 pM. The K_D for binding to human PlGF-2 is 39 pM.

12.3. Pharmacokinetics

EYLEA is administered directly into the vitreous to exert local effects in the eye.

Absorption/Distribution

Aflibercept is slowly absorbed from the eye into the systemic circulation after intravitreal administration. In a pharmacokinetic substudy with frequent sampling, maximum plasma concentrations of free aflibercept (systemic C_{max}) were low, with a mean of approximately 0.02 mcg/mL (range 0 to 0.054) within 1 to 3 days after a 2-mg intravitreal injection, and were undetectable two weeks following dosage in almost all patients. Aflibercept does not accumulate in the plasma when administered intravitreally every 4 weeks. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than a 100 fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF.

Elimination

Free aflibercept binds VEGF to form a stable, inert complex. As with other large proteins, both free and bound aflibercept are expected to be cleared by proteolytic catabolism.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at doses ranging from 3 to 30 mg/kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. Based on C_{max} and AUC for free aflibercept observed at the 3 mg/kg intravenous dose, the systemic exposures were approximately 4900-fold and 1500-fold higher, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible.

13.2 Animal Toxicology and/or Pharmacology

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at systemic exposures in excess of the maximum human exposure. The systemic exposure based on C_{max} and AUC for free aflibercept were approximately 200- and 700-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg. At the No Observed Adverse Effect Level

(NOAEL) the systemic exposure was 42- and 56-fold higher based on C_{max} and AUC, respectively.

Similar effects were not seen in clinical studies [*see Clinical Studies (14)*].

14 CLINICAL STUDIES

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with EYLEA) in the two studies (VIEW1 and VIEW2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 3 initial monthly doses (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); 3) EYLEA 0.5 mg administered every 4 weeks (EYLEA 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). Patient ages ranged from 49 to 99 years with a mean of 76 years.

In both studies, the primary efficacy endpoint was the proportion of patients in the Per Protocol Set who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Data are available through week 52. Both EYLEA 2Q8 and EYLEA 2Q4 groups were shown to have efficacy that was non-inferior and clinically equivalent to the ranibizumab 0.5 mg Q4 group.

Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in Table 2 and Figure 14 below.

Table 2: Efficacy Outcomes at Week 52 (LOCF) in VIEW1 and VIEW2 Studies

	VIEW1			VIEW2		
	EYLEA 2 mg Q8[a]	EYLEA 2 mg Q4	Ranibizu-mab 0.5 mg Q4	EYLEA 2 mg Q8[a]	EYLEA 2 mg Q4	Ranibizu-mab 0.5 mg Q4
Full Analysis Set	N=301	N=304	N=304	N=306	N=309	N=291
Mean number of active injections over 52 weeks	7.6	12.5	12.1	7.7	12.6	12.7
Efficacy Outcomes						
Proportion of patients who maintained visual acuity[b] (%) (<15 letters of BCVA loss)	95.1%	95.1%	94.4%	95.6%	95.6%	94.4%
Difference[c] (%) (95% CI)[d]	0.7 (-3.1, 4.5)[e]	0.7 (-3.1, 4.4)[e]		1.1 (-2.6, 4.8)[e]	1.2 (-2.5, 4.9)[e]	
Mean change in BCVA as measured by ETDRS letter score from Baseline	7.9	10.9	8.1	8.9	7.6	9.4
Difference[c] in LS mean (95% CI)[d]	0.26 (-1.97, 2.49)	3.15 (0.92, 5.37)[f]		-0.90 (-3.06, 1.26)	-1.95 (-4.10, 0.20)	
Patients who gained at least 15 letters of vision from Baseline (%)	92 (30.6%)	114 (37.5%)	94 (30.9%)	96 (31.4%)	91 (29.4%)	99 (34.0%)
Difference[c] (%) (95% CI)[d]	-0.4 (-7.7, 7.0)	6.6 (-1.0, 14.1)		-2.7 (-10.2, 4.9)	-4.6 (-12.0, 2.9)	

BCVA = Best Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCF = Last Observation Carried Forward (baseline values are not carried forward)

[a] After treatment initiation with 3 monthly doses

[b] Per Protocol Set

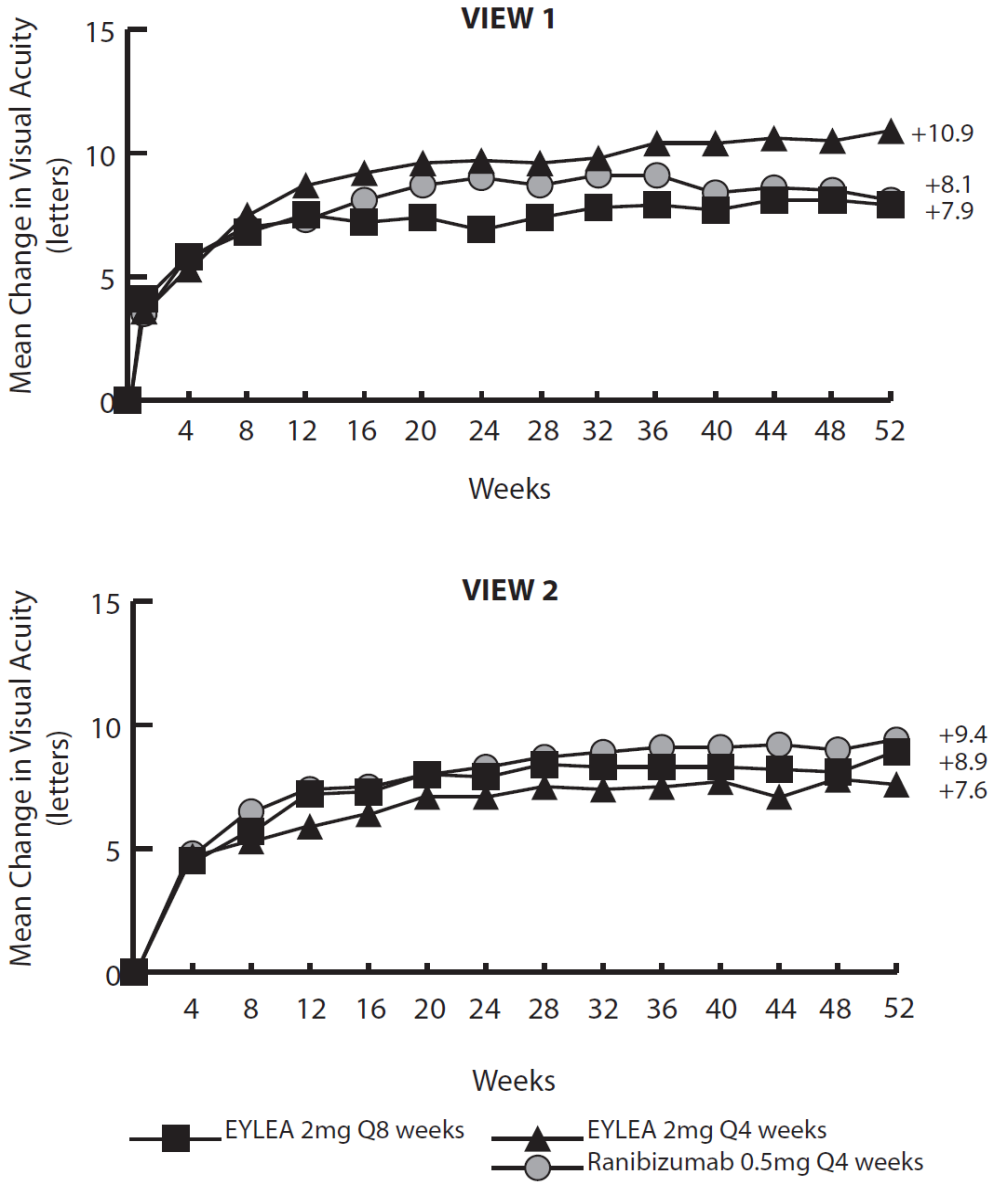
[c] EYLEA group minus the ranibizumab group

[d] 95.1% CI for VIEW1

[e] A confidence interval lying entirely above -10% indicates a non-inferiority of EYLEA to ranibizumab.

[f] $p<0.01$. A confidence interval lying entirely above zero indicates a statistical difference favoring EYLEA.

Figure 14: Mean Change in Visual Acuity from Baseline to Week 52 in VIEW1 and VIEW2 Studies



Efficacy results in all evaluable subgroups (e.g., age, gender, race, baseline visual acuity, lesion type, and lesion size) in each study and in the combined analysis were consistent with the results in the overall populations.

16. HOW SUPPLIED/STORAGE AND HANDLING

EACH PRE-FILLED SYRINGE OR VIAL IS FOR SINGLE EYE USE ONLY. EYLEA is supplied in the following presentations. [*See Dosage and Administration (2.3) and (2.4).*]

NDC NUMBER	CARTON TYPE	CARTON CONTENTS
61755-005-01	pre-filled syringe	one sterilized blister pack containing one single-use, sterile, 1-mL, pre-filled, glass syringe delivering 2 mg in 0.05 mL (50 microliters) aflibercept ophthalmic solution one 30-gauge x ½-inch injection needle for intravitreal injection one package insert
61755-005-02	vial	one single-use, sterile, 3-mL, glass vial containing a 0.278 mL fill of 40 mg/mL aflibercept ophthalmic solution one 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents one 30-gauge x ½-inch injection needle for intravitreal injection one 1-mL syringe for administration one package insert

Storage

EYLEA should be refrigerated at 2°C to 8ºC (36°F to 46ºF). DO NOT FREEZE. Do not use beyond the date stamped on the label.

Pre-filled syringes containing EYLEA should be protected from light. Store in the original carton until time of use.

Vials containing EYLEA should be protected from light. Store in the original carton until time of use.

17. PATIENT COUNSELING INFORMATION

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Patients should be advised not to drive or use machinery until visual function has recovered sufficiently.

In the days following EYLEA administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patient should seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

REGENERON

Manufactured by:

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